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HEART DISEASE AS A CAUSE OF MATERNAL DEATH*

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(From the Brooklyn Committee on Maternal Welfare)

THE role of heart disease as a factor in the maternal death rate cannot be stated with certainty. Nor is the incidence of rheumatic heart disease during the reproductive period of life known. Incidence calculated indirectly from reported deaths and comparison[1] between the death rate among parturient women and that among the remaining female population of childbearing age are of little value. In New York City,[1] however, for 1930-1932 there were 173 deaths from cardiac disease in 348,310 deliveries, a mortality rate of 50 per 100,000. Jensen[2] believed that this figure indicated fairly well the magnitude of the problem. There were 171,174 live births in New York City in 1947 and 230 maternal deaths, 42 of which were attributed to heart disease.[3] The mortality rate was 24.5 per 100,000.

Correlations of heart disease with the maternal death rate cannot be made from the usual tables of vital statistics. More than one cause is mentioned on a great many certificates of death, yet but one cause is tabulated. In vital statistics practice heart disease associated with pregnancy has long been allocated either to a puerperal or to a nonpuerperal cause, or has been coded as a secondary or associated cause of death and so has disappeared entirely from the record. Prior to 1949, selection of the cause of death was made arbitrarily by rules for uniform treatment of joint causes.[4] Since then the statement of the certifying physician as to the underlying cause of death has been largely accepted by the statistician.[5]

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In Brooklyn, for instance, from 1937 to 1949, but 34 per cent of all the deaths in which both cardiac and puerperal causes were mentioned on the certificate were allocated by the statistician to heart disease; 66 per cent, assigned by rule to puerperal causes, escaped tabulation as heart disease. Since 1949, however, approximately 90 per cent of the deaths in which cardiac and puerperal causes were associated, have been allocated to heart disease, thus helping to lower the puerperal death rate considerably.

Actually, there is no way of discovering the mortality of heart disease in childbirth unless we know how often it contributes to death as well as causes it. In 1940 when this tabulation was last made in the United States,[6] heart disease contributed to death in 7.1 per cent of the deaths allocated to disease of pregnancy, childbirth, and the puerperium (8.876). If deaths in childbirth which were assigned to diseases of the heart should be added to this number, the proportion of deaths in which heart disease was either primary or secondary would rise to 8.8 per cent. And when all the deaths associated with childbirth (13,228) were studied, heart disease was found to be a factor in 6.0 per cent of them.[7]

Knowledge of heart disease complicated by pregnancy is derived for the most part from maternal death studies and reports of experiences with well-controlled clinical material. Jensen in his classic work on the relation between heart disease and pregnancy found but 510 cases which were fatal during or soon after the period of gestation. Bunim and Appel,[8] listing all the deaths among pregnant women with rheumatic heart disease reported in the literature from 1936 until 1948, found but 217 cases. Quite understandably, deaths reported in maternal mortality studies were not found by them. At any rate, the total number of deaths reported in the literature is comparatively insignificant.

Through the cooperation of the Commissioners of Health, the Brooklyn Committee on Maternal Welfare has, since 1937, been supplied with a copy of the death certificate in the case of every woman who died in Brooklyn from any cause whatsoever associated with pregnancy, whether death was allocated to a puerperal cause or not. These transcripts have been routinely amplified by case reports. In many cases, additional data have been added after group discussion. From 1942 to 1949 maternal mortality reports[9-15] from Brooklyn paid particular attention to cardiac disease.

The aim of this detailed account of 176 deaths (10 of the patients were nonwhite), is a restatement of the problem. All case reports have been strictly scrutinized. They are clinical, it is true, yet in the main observations were made by very competent observers. Clinical diagnoses are reasonably reliable when heart disease is severe enough to cause death. Reports of autopsies were found in 19 per cent of the cases.

Pregnancy, of course, cannot be made a matter of record, yet in New York City all terminated pregnancy is reportable. Thus, abortions, ectopic pregnancies and patients who die undelivered are included. The trend of mortality from heart disease associated with pregnancy in Brooklyn, City of New York, over a period of fifteen years is shown in five-year cycles in Table I. The mortality ratios per 100,000 may be compared with Jensen's estimate of 50 nearly two decades ago.

TABLE I. MATERNAL MORTALITY ASSOCIATED WITH HEART DISEASE
171 DEATHS—BROOKLYN

TIME PERIOD	1937-1941	1942-1946	1947-1951
Terminated pregnancies (in thousands)	219	282	322
Deaths from heart disease (primary and secondary)	67	54	50
Mortality ratio	30.6	19	15.5

The large number of deaths available for analysis, one-third as many as reported by Jensen, seemed to call for as full an audit, so his method will be rather closely followed. All the maternal deaths associated with heart disease which occurred in Brooklyn from 1937 to 1952, inclusive, are classified in Table II.

The number of cases of combined mitral and aortic disease is less than one-third the number of cases of mitral disease alone. No case was reported as simple mitral regurgitation.

The diagnosis of pancarditis in 5 cases was based upon autopsy findings in 4 cases and upon pericarditis with effusion and electrocardiographic study in the other. The oldest patient was 28 years of age; 3 died undelivered.

Auricular fibrillation was reported in 11 cases. Eight women died during their first pregnancy; decompensation had occurred in 3 of them in their previous pregnancy, and but one patient went to term; but 3 patients were less than 25 years of age. Cesarean section was performed twice in this group of cases.

Diagnosis in the cases of aortic stenosis and tricuspid disease was proved at autopsy.

TABLE II. DIAGNOSIS IN 176 DEATHS

A. Rheumatic heart disease			145 cases	82.4%
Valvular lesions:				
Mitral disease alone		80		
Aortic disease alone		1		
Mitral and aortic disease		26		
Mitral and tricuspid disease		1		
Not recorded		32		
Pancarditis		5		
Associated lesions:				
Auricular fibrillation	11			
Subacute bacterial endocarditis	5			
Acute bacterial endocarditis	6			
Hypertension	1			
Complete heart block	1			
B. Acute bacterial endocarditis (nonrheumatic)			5	
C. Congenital heart disease			6	3.4%
Ventricular septal defect		3		
Auricular septal defect		1		
Auricular septal defect and mitral stenosis		1		
Patent ductus arteriosus		1		
D. Hypertensive heart disease			15	8.5%
E. Coronary occlusion			3	
F. Kyphoscoliotic heart disease			1	
G. Rupture of aorta			1	

Age

Four patients with rheumatic heart disease were very young; the youngest, 16 years of age, died of eclampsia. A patient 18 years of age with mitral and aortic disease who had congestive failure in the fourth month and again

in the fifth and the sixth months died undelivered in the eighth month of pregnancy. Two young women, hardly 18 years of age, who had never had decompensation, died after cesarean section.

In the group of 145 women with rheumatic heart disease, 111, or 76.5 per cent, were 25 years of age or older and half were more than 30 years of age. In the hypertensive group 85 per cent of the patients were more than 30 years of age.

In Table III all 176 deaths are distributed according to age.

TABLE III. AGE AT DEATH

AGE IN YEARS	TOTAL CASES	TYPE OF HEART DISEASE			
		RHEUMATIC	ACUTE BACTERIAL	CONGENITAL	HYPERTENSION AND OTHER
16	1	1			
18	3	3			
20-24	33	30		2	1
25-29	42	38	2		2
30-34	50	42	2	2	4
35-39	34	24	1	1	8
40-45	13	7		1	5
Total	176	145	5	6	20

Parity

In death associated with rheumatic heart disease, increasing parity was not a factor in death since one-half of the deaths (72) took place during or soon after the first pregnancy. Data which appear to show that increase in parity is significant actually point to the importance of age as a factor in mortality. The effect of a concurrent increase in age and parity in rheumatic heart disease may be seen in Table IV.

TABLE IV. AGE AND PARITY IN RHEUMATIC HEART DISEASE

AGE IN YEARS	TOTAL CASES	PARITY					
		0	I	II	III	MORE THAN III	NOT STATED
16	1	1					
18	3	3					
20-24	30	24	5	1			
25-29	38	27	6	1	2	2	
30-34	42	12	12	7		6	5
35-39	24	4	9	5	1	3	2
40-45	7	1	2	1	1	2	
Total	145	72	34	15	4	13	7

Fetal Mortality

Fetal mortality, as shown in Table V, was high—62 per cent in 176 cases, and 57 per cent in the rheumatic heart disease group. This may be compared with Hamilton's[16] 45.2 per cent in 42 deaths. Fetal loss in maternal death due to hypertensive heart disease was notable.

The fetus was undelivered or stillborn in 50.2 per cent of the group of cases of rheumatic heart disease. Intrapartum death was not due to intrapartum medication. Prematurity played a minor part as a cause of death since of the 7 viable infants in the neonatal death column 4 deaths might be attributed to cesarean section and another to premature separation of the placenta.

Stander, however, is quoted[17] as having shown that the only way in which cardiac disease may affect the infant loss is indirectly through the number of therapeutic abortions performed because of the cardiac disease.

TABLE V. FETAL MORTALITY

		OUTCOME OF THE FETUS							
		UNDELIV-ERED		BORN DEAD		NEONATAL DEATH		ALIVE	
	TOTAL	NO.	%	NO.	%	NO.	%	NO.	%
Rheumatic.—									
Less than 20 weeks	13	7		6					
20-28 weeks	26	15		7		4			
28 weeks and over	106	26		12		6		62	
			33		17.2		7		42.8
Acute bacterial	5	1		4					
Congenital	6					1		5	
Hypertensive	15	10*		5					
Other	5	5							
	176	64		34		11		67	

*One liveborn by postmortem cesarean section.

Postmortem Cesarean Section

In an effort to increase fetal salvage, cesarean section was performed on 11 women after death; 5 were primigravidas and 6 multiparas.

Abdominal delivery had been planned for 4 patients who were admitted to the hospital for a rest period two weeks before term, but congestive failure and death supervened. Two women near term died in the street; neither was known to have been in failure. One, 28 years of age, had had rheumatic fever twelve years before; the other, 32 years of age, died of rupture of the aorta.

In 3 cases the fetus was born alive, but 2 of these babies died within an hour. Only one infant survived; brief clinical data of this case are of interest:

A 38-year-old primigravida, a known hypertensive patient for years, was admitted to the hospital in coma during the thirty-second week of pregnancy. Her blood pressure was 300/100 when death occurred five hours later. Cesarean section was performed shortly after death. Autopsy showed massive hemorrhage in the medulla, midbrain, and pons; marked hypertrophy of the left ventricle of the heart indicated cardiovascular disease of long duration.

Abortion

Delivery occurred prior to the twenty-eighth week of pregnancy in 18 cases; 17 patients had rheumatic heart disease and 1 had hypertensive heart disease; 2 were nonwhite. The average age was 28 years.

In the spontaneous group (10 cases) one abortion occurred at 10 weeks, the others between the sixteenth and the twenty-fourth weeks. Congestive failure preceded abortion, and death and abortion were almost simultaneous. In the criminal abortion group (6 cases) one death followed hemorrhage and shock, and 5 were due to acute bacterial endocarditis. The essential data of 2 therapeutic abortions are:

CASE 1.—A secundipara, aged 31 years, who had congestive failure in her second pregnancy, became decompensated in the eighth week of her third pregnancy. Under open ether anesthesia curettage was performed with estimated blood loss of 200 c.c. Death an hour later was due to pulmonary edema.

CASE 2.—A primigravida, aged 23 years, suffered pulmonary infarction in the fourth week of pregnancy. After 40 days in bed in the hospital, abdominal hysterotomy and tubal ligation were performed under local anesthesia. Death 11 days later was due to pulmonary infarction.

If the patient is in failure, or if cardiac reserve is low, abortion will but aggravate the situation. It has been shown that if continuous hospitalization is insisted upon, interruption of pregnancy will be unnecessary.[18]

Cesarean Section

Cesarean section was performed on 30 women with rheumatic heart disease and 4 with congenital cardiac lesions; 22 were primigravidas. Operation was performed before the thirty-sixth week in 10 cases, and between the thirty-sixth and the fortieth weeks in 24 cases.

In 24 cases heart disease was the sole indication for operation. The type of anesthesia selected was local infiltration (16 cases), spinal (11 cases), and inhalation (6 cases); one operation was performed without anesthesia upon a moribund patient. All but 7 of these women had been in congestive failure at some time ante partum; and all but 7 were in failure or had been in failure shortly before operation; 6 patients were sterilized; 7 women died on the operating table.

In 7 cases decompensation had never occurred; death was due to anesthesia (3 cases), embolism (2 cases), infection (1 case) and congestive failure (1 case).

Mild pre-eclampsia was present in 3 cases, and 2 patients had been delivered abdominally before. The indication in 2 cases was placenta previa; one of these patients was in failure when operated upon, and the other who had never suffered decompensation died from spinal anesthesia. A primigravida 18 years of age who had never been in failure died shortly after administration of 50 mg. of procaine for spinal anesthesia. A primigravida 40 years of age died in failure near term an hour after cesarean section for breech presentation. Abruptio placentae was the indication for operation in a patient who died of bacterial endocarditis nearly two months later.

The causes of death and the fetal mortality are shown in Table VI.

TABLE VI. CESAREAN SECTION DEATH AND FETAL MORTALITY

CAUSES	NO.
Congestive failure	19
Embolization	3
Failure and embolization	3
Heart block	1
Bacterial endocarditis	2
Anesthesia	4
Intestinal obstruction	1
Peritonitis	1

Fetal mortality—26.5 per cent

TABLE VI A. DURATION OF PREGNANCY AND OUTCOME OF FETUS IN 34 CESAREAN SECTION DEATHS

DURATION OF PREGNANCY	TOTAL	DEADBORN	NEONATAL	ALIVE
26-31 weeks	5	1	3	1
32-40 weeks	29	3	2	24

Causes of Death

Heart disease was the primary cause of death in 160 cases. The obstetrician often finds it difficult to attribute death to a single cause yet congestive failure was clearly the immediate cause of death in 126 cases—78.8 per cent of the deaths due to heart disease or 71.6 per cent of all the maternal deaths associated with heart disease.

The role of anesthesia may be difficult to determine. It caused death in 5 cases; 4 women who had never been in failure died of spinal anesthesia for abdominal delivery; another whose compensation had been re-established after break in the sixth month died during ether anesthesia for cesarean section near term. Postanesthetic atelectasis preceded failure in 2 additional cases, and a death attributed to acute congestive failure during instrumental delivery may have been due to caudal anesthesia.

Hemorrhage contributed to death in many cases, and 6 women who had never been in failure actually died of shock. The remaining noncardiac causes of death, were eclampsia (1 case) intestinal obstruction (1 case) and infection (3 cases). The causes of death are set down in Table VII.

TABLE VII. CAUSES OF DEATH

PRIMARY CAUSE	TOTAL	CHRONIC RHEUMATIC ENDOCARDITIS	BACTERIAL ENDOCARDITIS		CONGENITAL	HYPERTENSIVE AND OTHER
			RHEUMATIC	NOT RHEUMATIC		
Congestive failure	126*	106	6	1	1	12
Embolism	22	11	3	4	4	
Pulmonary edema	5	2	2			1
Unknown, sudden	2				1	1
Cerebral hemorrhage	4					4
Rupture of aorta	1					1
Anesthesia	5	5				
Other non-cardiac	11	11				
Total	176	135	11	5	6	19

*Congestive failure contributed to death in 7 additional cases.

Congestive Heart Failure

The large number of deaths due to congestive heart failure make it important to learn when it first made its appearance in these 126 cases. The onset of failure showed fairly close correlation with the changes in cardiac output and blood volume generally accepted as common to pregnancy. The largest number of failures occurred in the fourth month, and nearly half (57) during the first half of pregnancy. The time is shown in Table VIII.

TABLE VIII. TIME OF FIRST CONGESTIVE HEART FAILURE (126 CASES)

DURATION OF PREGNANCY	NO. OF CASES
Second month	6
Third month	8
Fourth month	28
Fifth month	15
Sixth month	16
Seventh month	14
Eighth month	13
Ninth month	11
Term	4
Unknown	4
During labor	3
After delivery	4
Total	126

When pregnancy had been uneventful, congestive failure occurred so infrequently during labor and the puerperium that these cases deserve special mention. In 2 of these cases the actual cause of death may have been anesthesia.

CASE 1.—A primigravida, 27 years of age, who became dyspneic and cyanotic after 54 hours of labor, died undelivered 16 hours after failure.

CASE 2.—Under caudal anesthesia, heart failure and death occurred during forceps delivery.

CASE 3.—Death occurred during instrumental delivery after 8 hours of labor complicated by pulmonary edema.

Congestive failure first occurred during the puerperium in 4 primigravidas; 3 women died within 24 hours of instrumental delivery; 2 had suffered considerable blood loss. A primigravida 39 years of age who had been delivered uneventfully died of a transfusion of 700 c.c. of blood on the eleventh day post partum.

When Jensen found "confusion complete regarding the relative dangers of the various phases of gestation," he studied the time of death in relation to gestation and delivery in 462 fatal cases. Since no similar analysis of any considerable number of cases has been published since that time, a comparable study of 145 deaths in the course of rheumatic heart disease appears in Tables IX and IXA.

TABLE IX. DEATH IN RELATION TO DELIVERY AND PERIOD OF GESTATION, 145 CASES OF RHEUMATIC HEART DISEASE

MONTH OF GESTATION	DIED UNDELIVERED	PREMATURE DELIVERY & DEATH DURING NATURAL PERIOD OF GESTATION	TOTAL DIED DURING NATURAL PERIOD OF GESTATION
2	—	2	2
3	2	2	4
4	5	3	8
5	5	5	10
6	11	5	16
7	8	14	22
8	6	14	20
9	9	26	35
Term	3	—	3
Total	49	71	120

TABLE IX A. LAPSE OF TIME BETWEEN DELIVERY AND DEATH

Less than 1 hour	14	Second day	7	Second week	13
1- 2 hours	5	Third day	4	Third week	4
2- 3 hours	3	Fourth day	3	Fourth week	3
3- 6 hours	6	Fifth day	2	Sixth week	3
6-12 hours	11	Sixth day	1	Eighth week	3
12-14 hours	9	Total, first week	65	Third month	5
Total, first day	48			Total after delivery	96

It will be seen that about one-third of these women died undelivered. Nearly two-thirds survived delivery, but 74 per cent of these delivered prematurely before they died, and so did not survive the natural period of gestation.

Bacterial Endocarditis

The diagnosis of bacterial endocarditis, acute and subacute, was made in 16 cases. All but 5 of these women were known to have rheumatic heart disease. Only 3 infants survived. Diagnosis was proved by autopsy (10 cases)

or by report of fever, enlarged spleen, and petechiae. Blood culture was positive for *Streptococcus viridans* (4 cases), *Streptococcus hemolyticus* (5 cases), Enterococcus (1 case), and *Staphylococcus aureus* (1 case). The patients were equally divided in the age groups 20 to 30 years and 30 to 40 years.

In the subacute group (*Streptococcus viridans*) of 4 cases a young woman who had congestive failure during the fourth month died undelivered ten weeks later after hemiplegia; blood cultures were positive. According to Davis,[19] who reported a case in 1947, Stander had been able to find reports of but 18 cases of subacute bacterial endocarditis during pregnancy. Another patient who had congestive failure in the sixth month died two months after cesarean section at term; 2 deaths followed spontaneous delivery complicated by phlebitis. The average duration of illness was fifty-eight days; all were known to have rheumatic heart disease. Respiratory infection preceded failure in 2 cases. The last death was reported in 1949.

In the 12 cases of acute bacterial endocarditis, rheumatic heart disease was present in 6 cases. The duration of illness varied from 3 to 13 days. Other than induced abortion (6 cases) the causes were postpartum phlebitis, pyelitis, and respiratory infection. When thrombophlebitis is present, either in the placental site or elsewhere, neither antibiotics nor chemotherapy may be relied upon for cure.

Congenital Heart Disease

Congenital heart disease accounted for 6 deaths, all in excellent hospitals, and in every case obstetricians and cardiologist had cooperated in the care of the patient. In every case the diagnosis was well established. Essential data appear in Table X.

TABLE X. CONGENITAL HEART DISEASE (6 DEATHS)

AGE	PARITY	ANTEPARTUM FAILURE	DELIVERY	TIME OF DEATH	CAUSE
19	0	6 months	Spontaneous*	7 days	Pulmonary embolism
23	0	3 months	Abdominal	24 hours	Pulmonary embolism
30	0	4 months	Abdominal	On table	Circulatory shunt
30	i	2 months	Abdominal	10 days	Pulmonary embolism
35	i	None	Forceps	18 hours	Congestive failure
40	ii	None	Abdominal	27 days	Hemiplegia

*Neonatal death.

Since the circumstances of a comparatively small number of puerperal deaths from congenital heart lesions have been reported, brief notes of these deaths are presented.

CASE 1.—After spontaneous delivery in the thirty-seventh week of pregnancy a 19-year-old primigravida with a ventricular septal defect had postpartum hemorrhage of about 600 c.c. A blood transfusion of 500 c.c. administered on the fourth day was promptly followed by auricular flutter. Cyanosis first observed on the seventh day suddenly deepened the next day and death occurred within ten minutes.

CASE 2.—A primigravida, aged 23 years, with patent ductus arteriosus, had cyanosis and dyspnea on slight exertion all her life. For three months before cesarean section was performed under spinal anesthesia congestive failure had frequently recurred. The day after operation, dyspnea and cyanosis were severe. Death was due to congestive failure.

CASE 3.—A primigravida 30 years of age with an interventricular septal defect had always had dyspnea and cyanosis. The last four months of pregnancy were spent in the hos-

pital. Cardiac reserve grew steadily less, and during the final six weeks oxygen was administered intermittently day and night. When pre-eclampsia developed, abdominal delivery was planned under fractional spinal anesthesia. Only 15 mg. of procaine had been administered when tachypnea and tachycardia occurred, with great agitation and apprehension, so operation was performed under local anesthesia and oxygen. Sudden death immediately after extraction of the fetus was attributed to circulatory shunt.

CASE 4.—A primipara, aged 30 years, with ventricular septal defect, was admitted to the hospital in congestive failure during the thirty-seventh week of pregnancy. Cesarean section was performed under local anesthesia a few days later. The patient was out of bed on the fourth day. On the tenth day cyanosis and dyspnea appeared, and she coughed up many large blood clots; Cheyne-Stokes respiration and death followed.

CASE 5.—During pregnancy a diagnosis of patent foramen ovale and aortic stenosis was made in a primipara 35 years of age who had never experienced congestive failure. At term she was delivered instrumentally under open ether anesthesia. Congestive failure quickly followed, and phlebotomy was performed. Death occurred within two hours. At autopsy a patent foramen ovale, aortic stenosis, and congestive failure were found.

CASE 6.—A multipara, aged 40 years, had been delivered twice abdominally. Known to have an auricular septal defect, she had never been in failure. Her third cesarean section was performed at term. Eight days later she suddenly became dyspneic, cyanotic, and pulseless. Heparin and continuous oxygen were administered from then on. Hemiplegia occurred a week later. Death occurred on the twenty-seventh day after operation.

Other Heart Disease

Heart disease other than rheumatic, bacterial, and congenital was mentioned on 62 certificates of death in the following terms: cardiac failure, decompensation, acute and chronic myocarditis, myocardial failure and insufficiency, cardiovascular and circulatory collapse, coronary thrombosis and occlusion, and hypertensive heart disease.

Since heart disease statistically is "taken to include all forms of heart disease (and undifferentiated heart disease) except syphilitic and thyrotoxic heart disease"[20] many certificates of puerperal death confuse the statistician and lay waste the statistics. The new certificates of death may remedy this situation.

In 42 of these 62 clinical reports no evidence of heart disease could be found. Death actually was due to hemorrhage (9 cases), toxemia (10 cases), bronchial asthma (1 case), anesthesia (5 cases), infection (2 cases), other well-defined causes (7 cases), and vague or unknown causes (8 cases). As a result of these reporting inaccuracies, 7 cases were officially allocated to heart disease as the primary cause of death and 25 cases to cardiac causes secondarily.

During the last trimester 7 women died suddenly at home undelivered. The physician attributed these deaths to coronary occlusion. In 4 cases the diagnosis was but a clinical impression. unsupported by any evidence. In 2 cases, however, diagnosis was made at autopsy, and electrocardiographic proof was good in the third.

A primigravida, 32 years of age, in the fortieth week of pregnancy died suddenly on her way to a clinic. The autopsy diagnosis was rupture of the aorta; degenerative changes were seen in the vessel wall. Another primigravida, 33 years of age, with kyphoscoliotic heart disease, bronchial asthma, and bronchiectasis, died in the thirtieth week of pregnancy, 15 hours after low forceps delivery; autopsy showed congestive failure.

There were 12 autopsies in the entire group of 20 cases. In 15 cases in which evidence of hypertensive disease was clear, fetal mortality was 100 per cent—10 undelivered and 5 spontaneously deadborn.

Comment

The Antepartum Period.—

The classification of patients according to their cardiac functional capacity was not recorded often enough to warrant any worth-while observation. When patients had been classified, however, in no case was change in rating mentioned, though conclusions as to diminution in functional capacity could readily be drawn from the case reports. Nor was it possible, in any considerable number of cases, to relate the date of the initial attack of rheumatic endocarditis to the time of death.

All through the records ran the thread of congestive failure during the antepartum period. Respiratory infection, pyelitis, and dental surgery were mentioned as precipitating causes but not often. Failure commonly occurred in the course of routine duties of the home without other known precipitating cause.

Women with complaints at least suggestive of early failure attended physicians' offices or made their way to clinics in one way or another, sometimes taking digitalis for months. Many repeatedly declined to enter the hospital. Or, after failure, they were treated for varying periods of time before admission to the hospital, only to remain there until compensation appeared to have been restored, then were sent home, perhaps in an ambulance, to return later for delivery and death. One patient had four antepartum admissions to the hospital. It was common for women who had entered the hospital for the conventional rest period two weeks before the expected date of delivery, or the day set for elective cesarean section, to fall into labor and die of congestive failure shortly afterward.

In many cases no consultation was had with an internist or, perhaps, but one, early in pregnancy; elective cesarean section was often enough the offspring of the conference. In the course of what was described as joint care at home by obstetrician and internist, women who were said never to have been decompensated died of congestive failure soon after admission to the hospital for the orthodox rest period or soon after premature delivery. It was not possible, however, to discover how often and under what circumstances the patient was seen by either physician. To reach the clinic or physician's office she was frequently called upon to travel some distance, involving considerable walking or fatiguing combinations of bus and subway.

Delivery and Puerperium.—

Congestive failure in all probability will not occur during labor nor will it follow delivery at or near term, if a break in compensation has not occurred ante partum. For delivery, the accepted precepts of good obstetrics should, of course, be followed. Good judgment must be exercised in the manage-

ment of protracted labor, abnormal presentation, and bony dystocia. The method of delivery is less important than the condition of the patient when she is taken to the delivery room. A set formula for the conduct of delivery is not rational, even the rule for interference at the time of full dilatation. Difficult instrumental delivery particularly when associated with hemorrhage is dangerous.

Placenta previa and abruptio placentae are dreadful problems. In placenta previa, however, the indication for hospitalization is clear and the period of observation generally agreed upon as good practice will enhance the safety of the cesarean section usually indicated. Blood transfusions, even small amounts, are not safe if the patient is in failure. In one case in this series transfusion was the cause of pulmonary edema, and in another auricular fibrillation followed. To lessen the hazard, administration of sedimented erythrocytes is advised; the volume of fluid will be reduced by half and the sodium content by three-fourths.[21]

High mortality associated with premature delivery and the expectation of saving the heart weeks of cumulative increase in the load on the circulation were the reasons for the flood of cesarean sections which has by now almost spent itself.

Abdominal delivery has long had the right of way, but just now it is out of favor. We need to reach more obstetricians and more internists, for it is important to know whether our contemporaries are not to some extent continuing the great tradition.

Pommerenke[22] has recently said, "Severe heart disease has for long been regarded as an ample reason for performing the cesarean operation. . . . The desire to sterilize the afflicted patient often weighs heavily in deciding on the section."

The risk of intervention is minimized by Levine[23] who believes that there is a sharp difference of opinion on cesarean section. "When, however," he says, "it has already been decided to perform sterilization a cesarean section should be done and the tubes tied off at the same time." To perform cesarean section in order to sterilize a patient who might otherwise have been delivered from below is not good sense.

The important issue is not whether abdominal delivery should be planned; it is rather whether cesarean section may be performed with safety on a patient with rheumatic heart disease. It has been said so often that cesarean section is contraindicated for cardiac disease, that this is often construed as a ban upon the operation for any patient with cardiac disease. What of the patient with cardiac disease when a valid indication for cesarean section exists? Will cesarean section be safe? It has not been possible to compare abdominal and pelvic delivery in exactly similar groups, and the effect on the circulatory system when the uterus has been suddenly emptied is not well understood. It appears, however, that if the patient should be close to term and has not been in congestive failure during pregnancy the operation should

be well tolerated. The hazards of hemorrhage and transfusion, anesthesia and infection are greater than in pelvic deliveries and must be taken into account.

Conclusion

It is difficult to talk dispassionately after a close-up achieved by a careful study of 176 maternal deaths and this faithful summary of the mortality experience of nearly two decades. The seamy chapter in obstetrics which was roughly opened with dogmatic generalizations and assumptions on cesarean section and interruption is now closed.

It is not true today, as was said but a short time ago, that obviously a radical improvement must come in the prevention of heart disease rather than in its management during the gestation.[24]

Congestive failure, not the lesion, is the significant factor in prognosis and treatment. Controllable factors are found in antepartum care more often than in the conduct of delivery. Good management implies more than observation at frequent intervals. As a matter of fact, these frequent clinic or office visits may be more than the patient should be asked to brave. Strict supervision is necessary. Tachycardia, insomnia, and dyspnea, though fairly common in normal pregnancy, are none the less symptoms of decrease in cardiac reserve and should give us more concern if the patient has heart disease. Cough, anemia, and excessive weight gain are important. Congestive failure should be anticipated, and hospitalization should be advised if the patient's environment or domestic responsibilities seem to warrant it.

In the event of any break in compensation, hospitalization should be insisted upon, and the patient should remain in the hospital until she has been delivered, no matter how far off the estimated date of delivery may be. In some circumstances this may not be possible, and the obstetrician will be forced to weight himself with grave responsibility. In this event, the patient's family should be made aware of the heavy risk of antepartum care at home after congestive failure. Inviting an internist to share the responsibility with him will not reduce the hazard. What is to be done about the cost of hospitalization for months before delivery? Well, almost nothing at present. We need to discover and develop methods for solving this problem. A few communities have found the solution. Pelvic delivery should be anticipated. Taken altogether, the problem of management of heart disease complicated by pregnancy becomes substantially less formidable if reduced to one of antepartum care.

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32 REMSEN STREET

THE USEFULNESS OF SERIAL VITAL CAPACITY DETERMINATIONS IN THE MANAGEMENT OF THE PREGNANT PATIENT WITH HEART DISEASE*

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THE serial measurement of the vital capacity during the course of pregnancy can be extremely helpful in the management of the patient with known or suspected heart disease. The inherent physiologic changes which occur in a normal pregnancy may cause dyspnea, ankle edema, and even apparent cardiac enlargement, so that these clinical symptoms and signs are not in themselves diagnostic of heart failure during pregnancy. Yet, because the prognosis is poor once the patient has developed frank pulmonary edema, it is important to make the diagnosis of heart failure as early as possible. It is also desirable to be able to distinguish between the dyspnea which is due to the changes in a normal pregnancy and the dyspnea which is caused by pulmonary congestion. The serial determination of the vital capacity during the pregnancy is a relatively simple means of detecting early pulmonary congestion and of diagnosing the cause of dyspnea.

Fourteen patients from the prenatal clinic at Temple University Hospital were followed with serial vital capacity determinations during pregnancy, labor, and the postpartum period. Eleven had rheumatic heart disease and, of these, 6 developed heart failure at some time during the course of the pregnancy. Three other patients had no heart disease, but had very much impaired pulmonary function following resection or chest deformity. Observations were begun in the first trimester in the case of 3 patients, in the second trimester in 7 patients, and in the last trimester in 4. The patients were seen on each regular prenatal visit. The management of the patient's cardiac status was conducted by the cardiologist and was not influenced by the vital capacity measurements.

Method

The vital capacity determinations were made and recorded on a modified Roth-Benedict water spirometer with the patient in a supine position. She was allowed to rest for a few minutes before the test was performed. After the patient had been breathing normally into the spirometer for a minute or two, she was asked to take as deep a breath as possible and to blow out as much as possible. This was repeated twice. The variation in serial vital capacity determinations on 15 normal, nonpregnant individuals, using the same apparatus, was ±150 c.c. Therefore, no changes were considered significant which were less than 300 c.c.

*Presented at a meeting of the Obstetrical Society of Philadelphia, Dec. 3, 1953.

Results

Patients With Heart Disease and Signs of Pulmonary Congestion at Some Time During the Pregnancy.—Six patients with rheumatic heart disease had objective signs of pulmonary congestion during pregnancy. These episodes were accompanied by marked decreases in the vital capacity.

A 25-year-old para ii, gravida iii, with rheumatic heart disease, cardiac enlargement, and mitral stenosis (Fig. 1, *a*), was first seen in the twenty-eighth week of pregnancy because of increasing exertional dyspnea, paroxysmal nocturnal dyspnea, cough, and hemoptysis. Fine, crackling râles were heard at both lung bases posteriorly and x-ray revealed moderate pulmonary congestion. After one week of treatment the vital capacity was 1,800 c.c. Two weeks later the patient was clinically better and was allowed to go home. The vital capacity had risen to 2,150 c.c. She developed an upper respiratory infection and returned in the thirty-second week with frank pulmonary edema requiring oxygen, digitalization, and diuretics. The vital capacity had fallen to 500 c.c. This represented a decrease of 1,600 c.c. After cardiac compensation had occurred, the vital capacity again rose to 2,100 c.c. and ultimately to 2,500 c.c. in the thirty-seventh week. She was hospitalized for the remainder of the pregnancy which was uneventful.

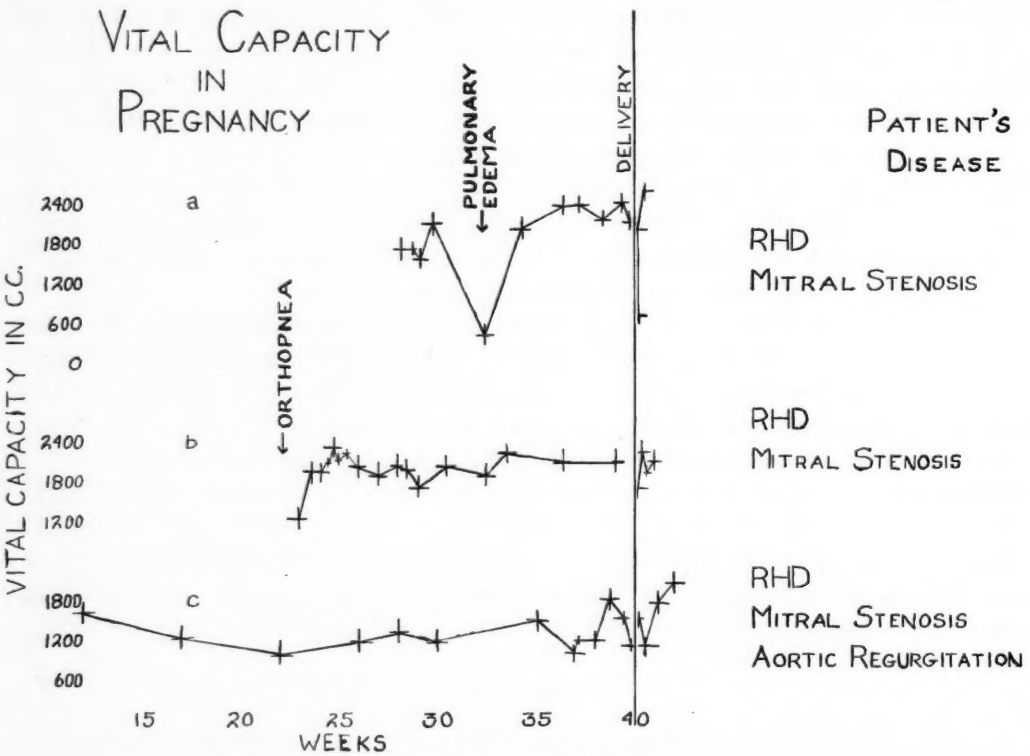

Fig. 1.—Serial measurements of vital capacity during pregnancy in 3 patients with rheumatic heart disease who showed signs of pulmonary congestion at some time during their course.

A 27-year-old para i, gravida ii, with rheumatic heart disease, cardiac enlargement and mitral stenosis (Fig. 1, *b*), was first seen in the twenty-third week of pregnancy with severe exertional dyspnea and orthopnea which had developed the week before with the onset of auricular fibrillation. She had not responded to digitalization. On admission she was orthopneic but the lungs were clear. X-ray showed pulmonary congestion. The initial vital capacity measurement was 1,300 c.c. After three days of bed rest, oxygen, and

further digitalization, her symptoms had improved and the vital capacity had risen to 2,000 c.c. (a 700 c.c. increase). After two weeks of bed rest and after the auricular fibrillation had been stopped with quinidine, the vital capacity rose to 2,500 c.c. The patient remained on partial bed rest throughout the rest of the pregnancy and had no further cardiac difficulty and no significant changes in the vital capacity.

A 21-year-old para 0, gravida i, with rheumatic heart disease, aortic regurgitation, and mitral stenosis (Fig. 1, *c*), was first seen in the tenth week of pregnancy. She had dyspnea only on severe exertion and had no signs of heart failure. Her initial vital capacity was 1,700 c.c. This gradually fell to 1,100 c.c. in the twenty-second week, then rose to its initial level by the thirty-fifth week. During this time she had no complaints. Ankle edema did develop at the thirty-third week, then cleared when the patient was put on a low-salt diet and a resin. About the thirty-seventh week she complained of dyspnea and had a 10 pound weight gain. The vital capacity had dropped again to 1,100 c.c. She was hospitalized and on bed rest the vital capacity rose to 1,900 c.c. in the thirty-eighth week. She developed orthopnea and tachycardia in the fortieth week just prior to the onset of labor. The vital capacity dropped from 1,900 c.c. to 1,200 c.c. She was digitalized and improved. The vital capacity rose to 1,700 c.c. four hours after treatment was begun.

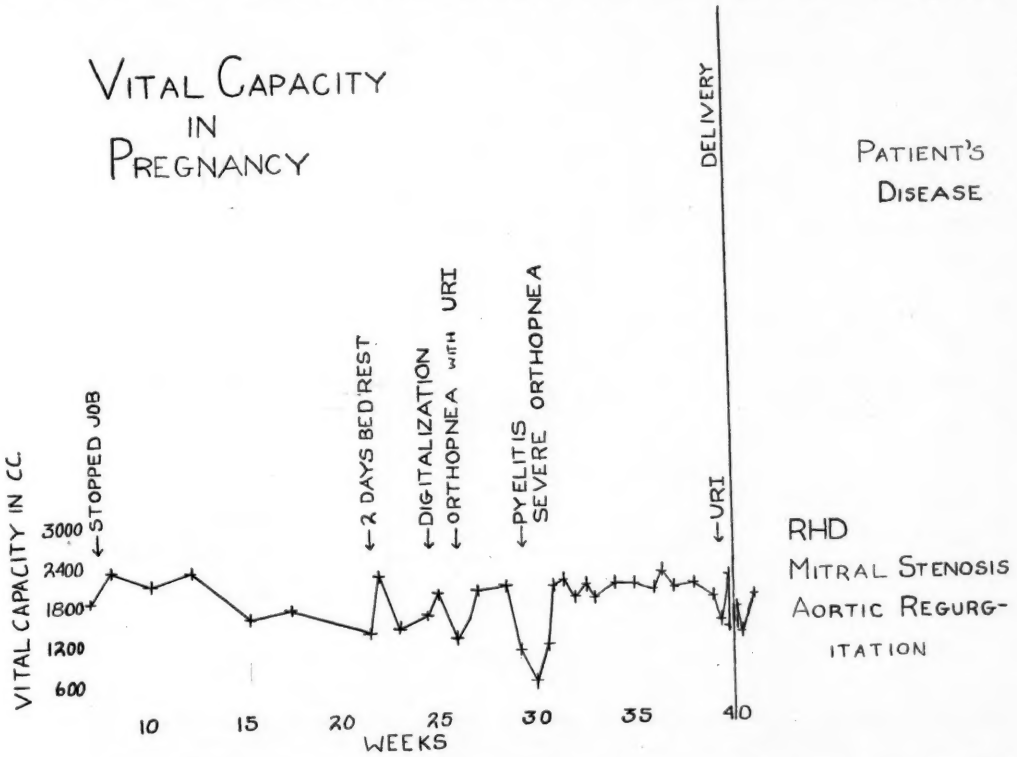

Fig. 2.—Serial measurements of vital capacity during pregnancy in a 21-year-old patient with rheumatic heart disease.

Two other patients with rheumatic heart disease, cardiac enlargement, and mitral stenosis were seen only during the last weeks of pregnancy. Both entered the hospital with dyspnea, orthopnea, and pitting edema of the ankles. After bed rest, mercurial diuretics, and digitalis, one patient lost 11 pounds and the other 7 pounds. Their symptoms of orthopnea, dyspnea, and ankle edema were relieved. An increase of 800 c.c. and 700 c.c., respectively, in vital capacity accompanied their improvement.

One patient, a 21-year-old para 0, gravida i, with severe rheumatic heart disease, cardiac enlargement, aortic regurgitation, and mitral stenosis, deserves special mention

(Fig. 2). The changes in vital capacity very nicely reflected and even anticipated the clinical changes which occurred. She was dyspneic on exertion at ten weeks. The vital capacity was 1,950 c.c. She stopped her job and the dyspnea improved. The vital capacity rose to 2,400 c.c. From the thirteenth to the twenty-first week she again had increasing dyspnea and paroxysmal nocturnal dyspnea. The vital capacity gradually dropped from 2,400 c.c. to 1,300 c.c. After two days of bed rest the dyspnea again improved; she lost 4 pounds; the vital capacity rose to 2,350 c.c. Up and about again, she developed orthopnea and was digitalized. During all this time the lungs were clear. During the twenty-ninth week she developed pyelitis and had severe dyspnea and orthopnea. The vital capacity dropped from 2,100 c.c. to 900 c.c. Fluids were forced. The dyspnea became worse. X-ray showed pulmonary congestion, râles were heard at the lung bases, and the vital capacity decreased further to 600 c.c. She improved over the next seven days and the vital capacity again rose to 2,100 c.c. She remained in the hospital for the duration of the pregnancy, and had no more difficulty until an upper respiratory infection developed in the thirty-ninth week. Again the vital capacity dropped but quickly improved.

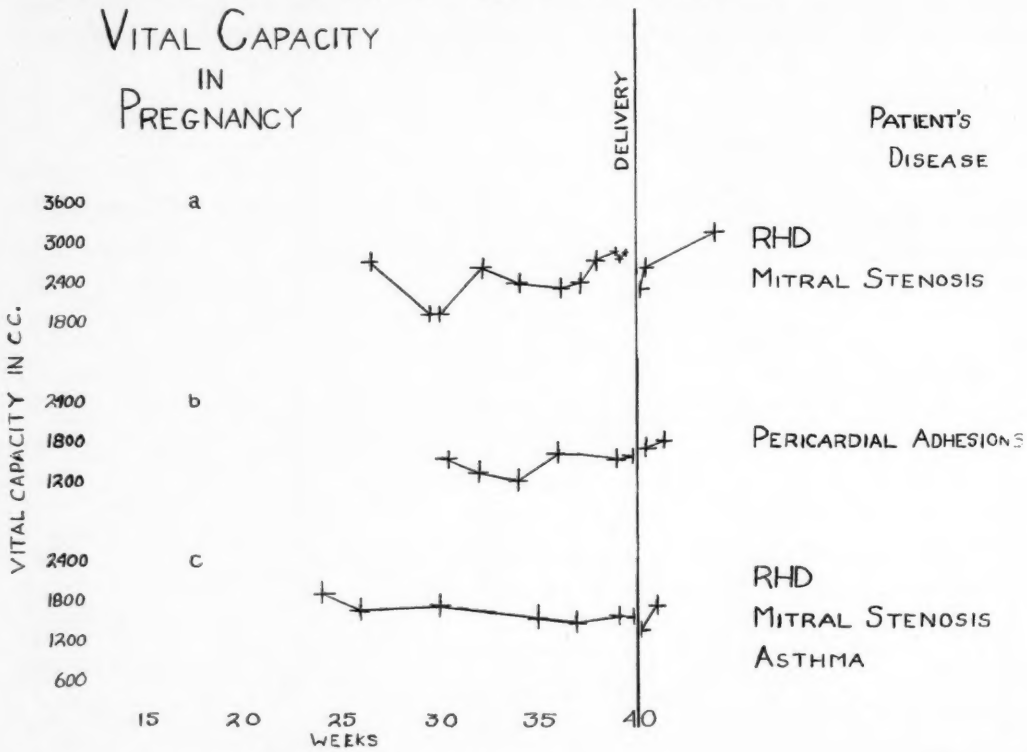

Fig. 3.—Serial measurements of vital capacity during pregnancy in 3 patients with heart disease who had no symptoms of heart failure during their course.

Patients With Heart Disease and No Heart Failure.—Five patients with heart disease went through pregnancy and delivery with no signs of heart failure. Four of these patients had rheumatic heart disease with mitral stenosis, one had aortic regurgitation in addiiton, and one patient had had constrictive pericarditis of undetermined etiology which had been treated surgically two years before. The records of 3 of these patients are seen in Fig. 3, *a, b, c.* Two of them (*a* and *b*) had decreases in vital capacity amounting to 300 to 800 c.c. between the thirtieth and the thirty-third week, which returned to the original level or higher before the thirty-sixth week. These decreases were not accompanied by any striking increase in dyspnea or other symptoms.

Patients With Loss of Pulmonary Volume and No Heart Disease.—Three patients had very much decreased ventilatory function due to severe kyphoscoliosis or pulmonary resection (pneumonectomy and lobectomy). As the pregnancy advanced, these patients developed increasing dyspnea. They had no orthopnea and the lungs remained clear. The patient with kyphoscoliosis had a renal calculus and had two severe attacks of pyelonephritis which required hospitalization. None of these patients had any respiratory difficulty during labor or delivery. As can be seen from Fig. 4, *a, b, c,* the initial vital capacity determinations on all 3 patients were much below normal—600 c.c., 1,000 c.c., 1,800 c.c.—and yet they did not vary significantly throughout the course of the pregnancy.

Behavior of Vital Capacity During Labor and Delivery.—There were 6 patients with rheumatic heart disease who had had evidence of heart failure during the course of pregnancy. Four of these patients developed dyspnea, orthopnea, and, in one case, basal râles and hemoptysis during the first stage

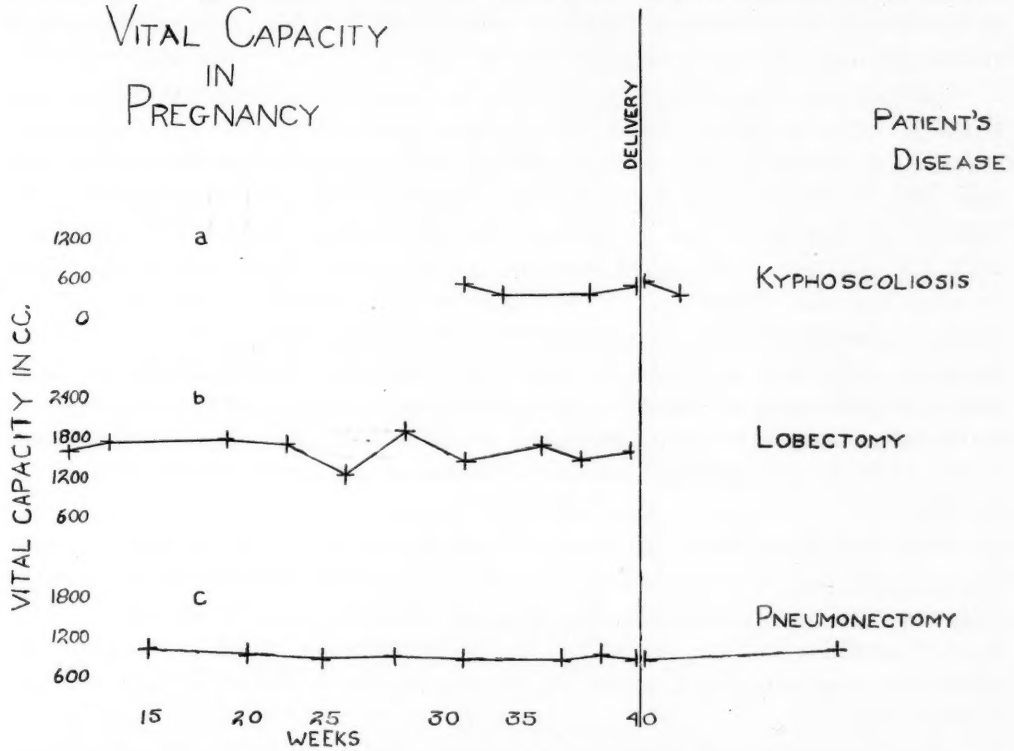

Fig. 4.—Serial measurments of vital capacity during pregnancy in 3 patients with loss of lung volume.

of labor. In all of them the vital capacity decreased markedly when the symptoms occurred. All responded to oxygen and morphine and in one case to digitalis. Both the symptoms and the vital capacity improved. After delivery of the placenta, the vital capacity again decreased and took twenty-four to forty-eight hours to return to the prelabor level.

In four patients who had rheumatic heart disease, but no clinical evidence of failure, there was no change in the vital capacity during labor. After delivery of the placenta the vital capacity dropped slightly (325 to 600 c.c.) and gradually returned to the predelivery level in twenty-four hours. This was not accompanied by symptoms.

No significant change occurred during labor and delivery in the vital capacity of either the patient with kyphoscoliosis or the patient with the pneumonectomy.

Comment

During the course of a normal pregnancy, the vital capacity either does not change or increases slightly as the pregnancy advances. At first there were many conflicting reports.[1, 2, 3] Alward[4] even claimed that as the pregnancy progressed the vital capacity decreased as much as 20 per cent. Other authors[5-8] found slight increases. In 1938, Thomson and Cohen[9] followed 34 normal women through pregnancy with careful vital capacity determinations, done with the patients standing, sitting, and lying down. They found that the vital capacity either stayed the same or gradually increased 200 to 300 c.c. up to the thirty-seventh to the thirty-ninth week, in all positions. These results were recently confirmed by Cugell,[10] who points out that the dyspnea which occurs during a normal pregnancy has no relation to changes in vital capacity.

On the other hand, the vital capacity is known to decrease in nonpregnant patients with left-sided heart failure and pulmonary edema.[11] Peabody[12] states that the decrease roughly parallels the degree of left-sided heart failure. The 6 women with rheumatic heart disease who developed heart failure during the course of the pregnancy showed similar changes. Concomitant with the episodes of increased dyspnea and orthopnea were marked decreases in vital capacity (Figs. 1, 2). The decreases ranged from 800 to 1,500 c.c. When pulmonary edema with audible râles was present, decreases in vital capacity amounted to 1,600 c.c. and 1,800 c.c. In these patients the vital capacity had begun to decrease from the twentieth week on and the two episodes of pulmonary edema occurred in the thirty-first and thirty-second weeks (Fig. 1, *a*, and Fig. 2) at the time when the blood volume may be at its height.[13]

The changes in the vital capacities of the patients with rheumatic heart disease who had no clinical evidence of heart failure are of interest. Three followed the normal pattern found in pregnancy (i.e., no change). Two showed significant decreases at the thirty-second week which were unaccompanied by any symptoms, again at the time when the blood volume may be at its height.

The 3 patients with restricted pulmonary function also developed increasing dyspnea during the course of the pregnancy, but, in contrast to the patients with heart failure, the vital capacities did not decrease, but followed a normal pattern.

Pulmonary congestion is not the only cause of a decreased vital capacity. The vital capacity is reduced by the following: loss of aerated lung tissue, paralysis of the respiratory muscles, and block of the airways. Such conditions, however, are either present when the patient becomes pregnant or can be easily diagnosed when they occur.

The reliability of the vital capacity readings is important. The patient must understand what is desired of her, and she must be made to feel that the

test is important to her. The same spirometer should be used each time, for changing resistances may change the vital capacity reading. The patient should always be in the same position. There may be a difference of 500 c.c. or more between the vital capacity standing and supine. When these conditions are met—a cooperative patient, the same spirometer, and the same position—it is possible to repeat the vital capacity reading on normal individuals at intervals of hours, days, and months with a variation of ±150 c.c. Done in this fashion, changes in vital capacity of more than 300 c.c. are significant.

Finally, it should be emphasized that an isolated vital capacity reading during pregnancy or during a period of dyspnea is worthless as an aid in determining the cause of the dyspnea or impending heart failure; a patient may have a vital capacity of 600 c.c. and be having no cardiac difficulty. It is the change in the vital capacity during the course of pregnancy which gives valuable information. In the patient with heart disease who has no other active pulmonary disease, a decreasing vital capacity means increasing pulmonary congestion. These changes may precede the onset of dyspnea and certainly precede frank pulmonary edema. If the patient with heart disease or suspected heart disease has increasing dyspnea, but no decrease in the vital capacity, then the dyspnea is not on a basis of pulmonary congestion and heart failure.

Summary

The serial measurement of the vital capacity during pregnancy is useful in the management of the patient with known or suspected heart disease. Early pulmonary congestion may be manifested by a decreasing vital capacity before the onset of dyspnea or frank pulmonary edema. Serial measurement of the vital capacity makes it possible to differentiate between the dyspnea of a normal pregnancy and the dyspnea caused by pulmonary congestion. In the normal pregnancy no decrease in vital capacity occurs; in pulmonary congestion the vital capacity decreases markedly.

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STUDIES OF THE FUNCTION OF EARLY HUMAN TROPHOBLAST

I. Observations on the Chemical Composition of the Fluid of Hydatidiform Moles*

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IN PRODUCING hydatidiform moles, Nature has offered one of her unique tissues to students of trophoblastic form and function. This interesting and occasionally tragic experiment of Nature results in a tissue which permits the study of purely trophoblastic function, unaltered or unmodified by the presence of an embryo. Studies aimed at elucidating the mechanism of transfer of chemical substances across the trophoblast have been, for the most part, concerned with comparing the concentration of various substances in cord blood and maternal blood at delivery. The interpretation of such data suffers to the extent that one is unable to differentiate the part played by the metabolic processes of the fetus from the possible regulatory functions of the placental trophoblast in producing differences in concentration of individual constituents in maternal and fetal blood. Since there is no embryo present in most cases of hydatidiform mole, it is likely that the fluid contained within the vesicles of such moles represents the product of trophoblastic function only. The interpretations of the studies presented in this report are based on this assumption.

Hydatidiform moles occur approximately once in every 2,000 pregnancies.[17] Hertig and Edmonds[16] have presented evidence that these abnormal pregnancies are the result of either the absence of, or the early death of, the embryo with a retention in the uterus of placental or chorionic tissue. In the normal course of events, the blood vessels which form in the chorionic villi (Stieve and Strube, quoted by Hertig[15]) join with the blood vessels of the embryo at about the fifth week of gestation or third week of development, at which time the embryonic heart begins to beat and the fetal-placental circulation is established. Even though blood vessels are originally present in molar villi, the early death or absence of the embryo prevents the establishment and function of the fetal chorionic circulation. In consequence, the vessels in the villi tend to disappear from the connective-tissue stroma. The chorionic tissue survives the death of the embryo since the life of the trophoblast is dependent (for the most part) on the integrity of the maternal and not the fetal circulation. The branches of the villi continue to swell and become bulbous and

*Aided by grants from the United States Public Health Service, American Cancer Society, Institutional Grant to Harvard Medical School, the American Cancer Society, Massachusetts Division, and the Charles H. Hood Foundation, Boston, Mass.

rounded rather than cylindrical in appearance. Most often this tissue is cast from the uterus at about 10 weeks of gestation and constitutes the pathological ovum of Hertig.[14] In most of these cases the swollen villi are visible only under the binocular dissecting microscope. If, however, as happens more rarely, the chorionic tissue is retained for a longer period of time, 17 weeks on an average, the villi become more greatly swollen, often attaining a size of from 2 mm. up to 3 cm. in diameter. These structures are numerous in the usual mole and could probably be counted in the thousands (Fig. 1). The enlargement of the villi is due to the accumulation of large amounts of fluid within the connective tissue of the villi. This fluid is essentially "edema" fluid and

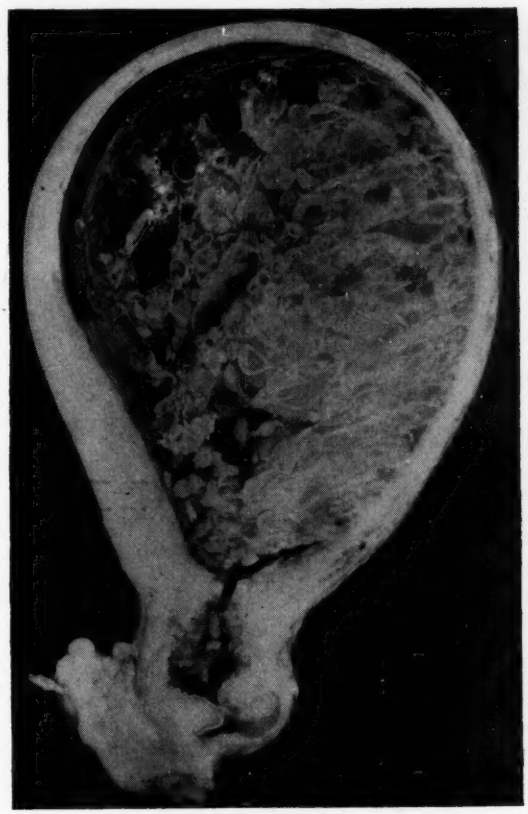

Fig. 1.—Hemisection of undelivered hydatidiform mole in utero. Near the fundus on the left side is a large blood clot. This specimen represents a fairly typical mole from the standpoints of volume of the entire specimen and of the size of the individual vesicles. (Photograph through the courtesy of Professor H. L. Sheehan, Liverpool, England.)

perhaps represents the most primitive edema (interstitial) fluid in the human organism. Histologically, the villus-vesicle is covered by an outer layer of syncytial trophoblast, beneath which lies a layer of cytotrophoblast. The inner lining of these cysts is composed of a myxomatous tissue which is rather thick and made up of scattered primitive mesenchymal cells with a large volume of intercellular "mucoid" material (Fig. 2). While the entire vesicle, especially the smaller ones, may be filled with mesenchyme, the larger vesicles

have a central cystic cavity filled with a clear fluid, some of which is coagulated by the usual histologic fixatives and is seen as an amorphous granular precipitate. It is the fluid from this central cavity which has been analyzed in this study.

While the trophoblast of most molar vesicles consists of the double layer of syncytium and cytotrophoblast (Fig. 3), there is some variation in the thickness of this layer due to varying degrees of trophoblastic proliferation. The cause of this trophoblastic growth is not known but it might be suggested that it is stimulated by the enlargement of the villus-vesicle, with a hypertrophy of the trophoblast to maintain the integrity of this membrane over the surface

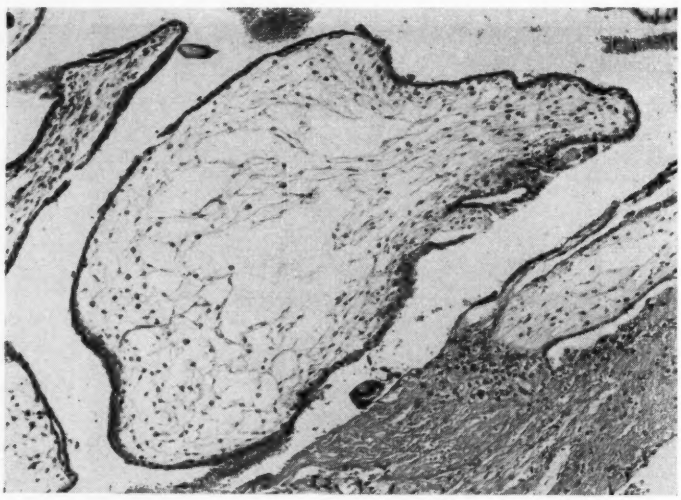

Fig. 2.—Photomicrograph of individual molar vesicle, with its trophoblastic covering, inner lining of mesenchymal connective tissue and central cavity. The cavity in this instance is smaller than those of the vesicles which are aspirated for their fluid contents. (Hematoxylin and eosin stain. BLI-S-39-327. ×50; reduced ⅙.)

of the villus. In some instances the trophoblastic growth amounts to more than hyperplasia and develops into an abnormally invasive tissue capable of invading the muscle of the uterus and/or of metastasizing to distant organs of the maternal host (Fig. 4). Histologically, this tissue is an anaplastic, pleomorphic, actively dividing malignant tumor. The transformation into cancer fortunately occurs in only 2.5 per cent of the cases, but some degree of histologic anaplasia is present in about half the cases. Also, invasion of the uterine wall by the so-called chorioadenoma destruens occurs in about 16 per cent of the cases, but does not appear to be malignant in the usual sense since it does not metastasize.

Therefore, it is clear that, while the fluid under analysis may be the pure product of the benign trophoblast, it is nevertheless tainted by either potential or actual malignant change.

Histologically, the molar vesicle presents the same anatomic features that the early ovum exhibits, except that there is no embryonic tissue embedded in the mesenchymal matrix. The fluid of hydatidiform moles is analogous to the fluid contained within the extraembryonic celom of the early ovum. This sim-

ilarity has led us to consider that the chemical constitution of the molar fluid is probably quite similar to that of the chorionic fluid, which is the immediate and intimate environment of the early embryo. For purpose of comparison in this respect, a few samples of chorionic fluid have been studied in addition to the mole fluid, and the results presented in a subsequent report.[22]

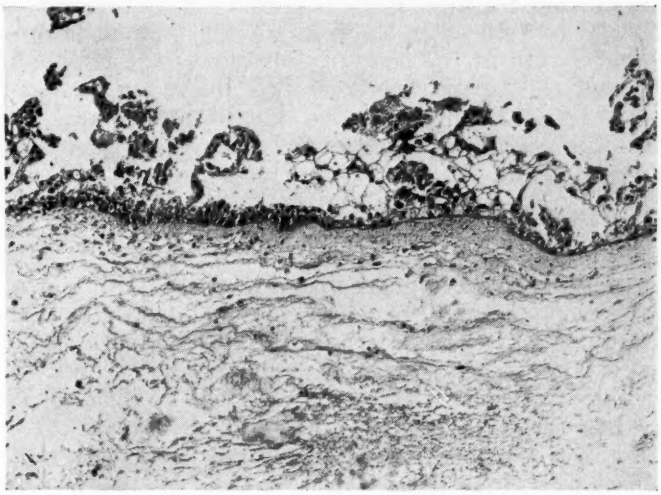

Fig. 3.—Photomicrograph of trophoblastic covering of a chorion from a specimen of hydatidiform mole. This consists largely of syncytial trophoblast with lacunar space formation. This tissue is identical with that covering many molar vesicles. (Hematoxylin and eosin stain. BLI-S-35-1123. ×50; reduced ⅕.)

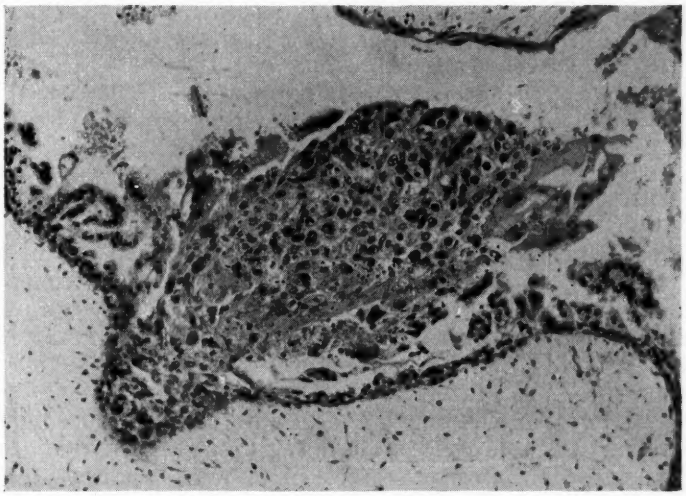

Fig. 4.—Photomicrograph of trophoblastic covering of molar vesicle illustrating the hyperplasia and anaplasia of both cyto- and syncytial trophoblast which is a prominent feature of many moles. This particular one was followed in 16 months by a fatal choriocarcinoma. (Hematoxylin and eosin stain. BLI-S-39-910. ×110; reduced ⅕.)

It is the purpose of this report to present observations on certain chemical constituents of the fluid of hydatidiform moles and to compare the concentrations with those of maternal serum and cord blood in an attempt to elucidate the function of early trophoblast.

Materials and Methods

During a period of two and one-half years we have been able to obtain 19 fresh moles for study.* The moles were removed by hysterotomy. In a few instances the patients had received or were receiving a blood transfusion. The mole vesicles were pierced by a needle and the fluid in the center aspirated into a syringe. The fluid from all the vesicles of any one mole was combined, centrifuged, and the supernatant fluid decanted. The fluid was then frozen in dry ice immediately and stored in the frozen state. Blood samples were taken from the antecubital vein at the time of delivery of the mole. The blood was allowed to clot and the serum was removed following centrifugation. The serum samples were also stored in the frozen state until analyzed. The amounts of fluid obtained from moles varied from 4 to 60 c.c., depending upon the size of the vesicles and the size of the mole. All the determinations could not be made in every case. Sodium and potassium were determined by internal standard flame photometry,[36] chlorides by iodometric titration,[34] and protein by the biuret method.[18]

The carbon dioxide and oxygen content of mole fluid, collected under oil, was determined in one case by the manometric technique. The nonprotein nitrogen was measured by the micro-Kjeldahl technique; uric acid by the method of Benedict[4] and creatinine by the method of Folin and Wu.[10] Glucose concentrations were determined by the method of Folin and Malmros[11]; calcium by the method of Clark and Collip[6]; total phosphorus by the method of Fiske and Subbarow[8]; alkaline and acid phosphatase by the method of Shinowara[31]; cholesterol and cholesterol esters by the Sperry-Schoenheimer[30] technique; total solutes by the freezing-point depression method; and protein-bound iodine† by the method of Barker.[3] The mole fluid and serum were also tested for the presence of blood group antigens and antibodies.† Amino acid nitrogen was determined according to the method of Van Slyke and associates.[33]† Ascorbic acid concentration was determined by the method of Roe and Kuether,[28] and inorganic iron by that of Bargen and Elvehjem.[2]

Results and Comment

Sodium, Potassium, Chloride, Total Protein, and Total Solutes.—

If the average values given in Table I can be accepted as representative of the composition of serum and mole fluid, then these fluids differ in their electrolyte composition and osmotic pressures. The sodium concentration is, on the average, 13 milliequivalents lower in mole fluid than in serum. This difference would be greater if the results had been calculated on the basis of millimoles per kilogram of water, since the total solute determinations indicate a higher concentration of water in mole fluid than in serum. The potassium is slightly higher in mole fluid than in serum. The chloride levels are lower in mole fluid. The total protein of mole fluid is almost one-sixth the concentration of serum proteins. In general, the osmotic activity of serum appears to be higher than that of mole fluid. These findings suggest that water is transferred across the trophoblast to the fetal side, or is retained on the fetal side against a higher osmotic pressure in the maternal blood surrounding the mole vesicle.

*We are pleased to acknowledge the generous cooperation of the members of the Boston Obstetrical Society, the New England Obstetrical and Gynecological Society, and the New England Pathological Society in this study.

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TABLE I. SODIUM, POTASSIUM, CHLORIDE, TOTAL PROTEIN AND TOTAL SOLUTES OF SERUM AND MOLE FLUID

	SODIUM (MEQ. PER LITER)		POTASSIUM (MEQ. PER LITER)		CHLORIDE (MEQ. PER LITER)		TOTAL PROTEIN (GM. PER 100 C.C.)		TOTAL SOLUTES (OSMOLES PER LITER)	
	SERUM	MOLE FLUID	SERUM	MOLE FLUID	SERUM	MOLE FLUID	SERUM	MOLE FLUID	SERUM	MOLE FLUID
1.	136	121	4.1	7.1	133	129	6.6	2.2	--	--
2.	143	134	4.8	7.9	136	111	5.0	1.7	--	--
3.	150	86	6.7	7.4	126	109	7.8	1.3	--	--
4.	140	122	4.8	--	102	104	--	--	--	--
5.	—	124	--	--	--	115	--	0.7	--	--
6.	118	126	3.4	6.4	98	71	7.3	1.1	--	--
7.	146	132	6.0	--	139	114	5.5	1.1	--	--
8.	130	94	6.8	5.7	107	104	4.4	0.5	--	0.25
9.	138	137	3.8	5.7	102	100	6.2	0.4	--	--
10.	134	134	3.7	6.6	111	116	6.1	0.9	--	--
11.	137	131	5.5	5.7	112	110	6.4	0.6	--	--
12.	134	140	5.4	7.9	102	107	6.2	1.2	0.27	0.29
13.									0.298	0.234
14.									0.243	0.270
15.									0.294	0.244
16.									0.292	0.257
17.									0.254	0.256
18.									--	0.237
Average	136	123	5.0	6.7	115	107	6.1	1.07	0.275	0.254
Maximum	150	140	6.8	7.9	139	129	7.8	2.2	0.298	0.29
Minimum	118	86	3.4	5.7	98	71	4.4	0.4	0.243	0.234

The behavior of the trophoblast of the term placenta with regard to potassium also seems to be similar to that of the early trophoblast of the mole. Cord blood has an average of 9.8 meq. per liter of potassium (Bakwin[1]) which amounts to an even greater difference from the level in the maternal plasma than that found in mole fluid. These findings suggest that both early and mature trophoblasts are able to concentrate potassium on the "fetal side." This might represent a useful process to the embryo and fetus since large quantities of this essentially intracellular electrolyte are used in the synthesis of tissues. An alternative explanation for the high potassium, as well as protein and phosphorus, might be that these substances are leaking from the cells of the molar vesicles.

The chloride levels in cord blood appear to be lower than in maternal blood (Miller[23]), which agrees with the lower chloride levels found in mole fluid. We are unable to explain the high average serum chloride concentration in this series, although Villee[35] has found a slightly higher than normal chloride level in normally pregnant women.

One of the major differences between mole fluid and cord blood lies in the sodium concentration, which is lower in mole fluid and higher in cord blood than in maternal plasma.[5, 23] Sodium averages 13 meq. less in mole fluid, whereas it is about 2 meq. higher in cord blood than in maternal blood. It has been demonstrated in rabbits and guinea pigs by Flexner[9] that sodium crosses the trophoblast at increasing rates of speed as gestation progresses. It may be that mature human trophoblast is more permeable to sodium than the early molar trophoblast. It might also be explained by the fact that mole fluid is essentially an interstitial connective-tissue fluid, which could be expected to have a lower sodium concentration than an intravascular fluid such as cord blood.

The low protein content of mole fluid agrees with observations on cord blood, which generally have shown a lower plasma protein on the fetal side (Pommerenke[27]).

It is of some interest to compare the electrolyte, water, and protein composition of this fluid with observations of edema, ascitic fluid (Table VIII) and connective-tissue fluid from tendon.[12, 13, 20]

From the standpoint of electrolyte composition, it is apparent that mole fluid is very similar to other interstitial fluids. All have a lower sodium and total protein than the serum. The protein content is closer to that of ascitic than of edema fluid. Mole fluid, however, appears to have a lower chloride content than ascitic or edema fluid. One total carbon dioxide content determination was done on mole fluid and was 24.5 meq. per liter, which, although slightly low, is in essential agreement with the carbon dioxide in other fluids.

The electrolyte pattern of tendon was found by Manery[20] to be essentially similar, except that the concentrations of potassium and phosphate were significantly higher than in other environmental fluids. In this respect mole fluid more closely resembles tendon than edema or ascitic fluid.

The mechanism of production of mole fluid must necessarily be different from that of other interstitial fluids. In the latter, hydrostatic pressure plays a role in causing the transfer of fluid from intravascular channels into the connective-tissue spaces. The vesicles of hydatid moles, however, are immersed in the blood contained within the intervillous space and are consequently subjected to the same pressure over their entire surface. While the blood pressure in the intervillous space surrounding the mole vesicles is not known, the anatomic arrangement suggests that such a mechanism is not responsible for transfer of fluid across this early trophoblastic membrane. In fact, the pressure gradient, if any, would seem to be in the opposite direction, since the vesicles continue to enlarge in spite of the inherent tonus of the uterine musculature. The observation that the mole fluid is hypotonic to plasma seems to remove the possibility that the steady expansion of the molar vesicles might be due to a higher osmotic pressure on the inside.

Although the composition of the fluid as determined in this study does not indicate the actual mechanism of transfer of fluid from plasma to the inside of the vesicles, it does seem to indicate that the water in the vesicle is retained against the force of a higher osmotic pressure in the surrounding plasma.

On the surface this might seem "unphysiological," since most fluids of the body that are separated by membranes are in osmotic equilibrium. There is ample precedent in past work on embryonic membranes, however, for such a conclusion. For example, the vitelline membrane of the egg of the hen separates two fluids of different physical and chemical composition. Needham[25] states " . . . there is a great difference in osmotic pressure (about 1.5 atmospheres). . . . The osmotic pressure difference is equivalent to about 2 Kg/sq. cm., but it is obvious that the membrane is not submitted to any such mechanical pressure. . . . Hevesy, Levi and Rebbe have shown that although heavy water quickly distributes itself between white and yolk when injected, radioactive sodium phosphate does not, but remains for long in the white.

"Straub and Hoogerduyn rightly considered that the Schreinemaker equations were inapplicable, and the distribution of ions in yolk and white is so different from what it would be on the Donnan equilibrium theory that the latter must be regarded as not alone sufficient to account for the case of the vitelline membrane of the birds' egg." Another example of fluids that are not isotonic, although part of the same organism, is that of the chick allantoic and amniotic fluids. Romanoff[29] states, "There is general agreement that the allantoic fluid is hypotonic to the amnoitic fluid throughout incubation." One need not have recourse to the lower animals to illustrate the point, since it has been demonstrated that human amniotic fluid at term is hypotonic to plasma. Therefore, the human amnion is also a membrane that divides two fluids that are not in osmotic equilibrium.

Further studies will be needed to elucidate the actual means by which the mole fluid is maintained hypotonic to plasma.

Nitrogenous Substances.—

Nonprotein nitrogen in general appears to be present in mole fluid in concentrations similar to those in maternal blood (Table II). This is also true of cord blood except that it is slightly higher in cord blood than in maternal blood. Uric acid concentrations are essentially the same in mole fluid, cord blood, and maternal blood.

Creatinine is somewhat higher in mole fluid than in maternal blood and this relationship appears to hold for cord blood also (Villee[35]). That cord blood contains a higher concentration of amino acids than maternal blood has been demonstrated by many investigators. The presence of almost twice the concentration of amino acid nitrogen in mole fluid, compared with the maternal serum, would indicate that the trophoblast concentrates amino acids on the "fetal side," and that this ability is shared by both early and mature trophoblast.

In addition to these determinations, one sample of mole fluid was tested by an immunologic technique* and found to have 1.0 Gm./100 ml. albumin with a total protein of 1.1 Gm./100 ml. The presence of albumin and/or protein in these concentrations suggests the possibility that proteins may cross the trophoblastic barrier in hydatidiform moles. This conclusion would be contradictory to that of Needham,[26] who stated that "good evidence exists that proteins can never pass the placental barrier in any mammal." The main evidence for this is that foreign protein injected into the maternal organism is not found on the fetal side after birth. Similarly, peptones appear to be unable to cross. Nevertheless, the interstitial fluid of muscle, edema fluid, and ascitic fluid all contain protein.

TABLE II. NONPROTEIN NITROGEN, URIC ACID, CREATININE AND AMINO ACID NITROGEN

	NPN (MG./100 C.C.)		URIC ACID (MG.:100 C.C.)		CREATININE NITROGEN (MG./100 C.C.)		AMINO ACID NITROGEN	
	SERUM	MOLE FLUID	SERUM	MOLE FLUID	SERUM	MOLE FLUID	SERUM	MOLE FLUID
1.	--	33	--	2.7	--	--	--	--
2.	--	23	--	2.9	--	0.41	--	--
3.	--	45	--	5.9	--	0.89	--	--
4.	15	25	2.2	2.3	0.34	0.99	--	--
5.	--	--	--	--	--	--	3.62	6.91

Protein-Bound Iodine.—

The observations presented in Table III suggest that protein-bound iodine, presumably thyroxin, is able to cross the barrier of the early trophoblast. In terms of micrograms per 100 ml. of fluid, the concentration in mole fluid is roughly one-sixth the concentration in the maternal serum, which is the same as that for total protein. On the other hand, in terms of micrograms per gram of protein, there seems to be a higher concentration on the "fetal side." According to McClendon and McLennan,[21] the protein-bound iodine content of cord blood also is lower than that of maternal serum, being sometimes half as much. The concentration of this material in cord blood is probably more related to the function of the fetus' own thyroid than to placental transmission. Nevertheless, Smith[32] states that clinical observation suggests that under some circumstances the placenta is able to transmit thyroid hormone either from the mother to the fetus or in the reverse direction.

*Dr. David Gitlin, The Children's Hospital, Boston, Mass.

TABLE III. PROTEIN-BOUND IODINE

	SERUM	MOLE FLUID
1.	--	0.75 μg/100 ml.
		1.5 μg/gram protein
2.	6.0 μg/100 ml.	0.94 μg/100 ml.
	0.86 μg/gram protein	0.99 μg/gram protein
3.	19.0 μg/100 ml.	3.62 μg/100 ml.
	2.7 μg/gram protein	5.4 μg/gram protein

Man[19] has demonstrated a close relationship between abortion and a decrease in the protein-bound iodine of maternal blood, which may be indicative of the importance of this hormone to the developing ovum.

The high level of protein-bound iodine in the maternal blood of the third patient in Table IV is related to the fact that this patient had signs of thyrotoxicosis with a basal metabolic rate of plus 50. It is interesting to note that the protein-bound iodine in her mole fluid was proportionately high also.

Blood Groups and Antigens.—

The observations presented in Table IV indicate that the ABO antigens do not cross the early trophoblast but that occasionally the agglutinins cross in small amounts. This is compatible with the finding of DeGowin, Hardin, and Alsever[7] that agglutinins are present in the blood of about one-half of newborn infants. They disappear after the first ten days of neonatal life. It has been shown that these agglutinins are identical with those of the mother and have presumably diffused through the placenta. The infant's own agglutinins appear subsequently.

TABLE IV. BLOOD GROUP ANTIGENS AND ANTIBODIES

MATERNAL BLOOD		MOLE FLUID	
ANTIGENS	AGGLUTININS	ANTIGENS	AGGLUTININS
1. A-Rh+	Anti-B	No A or B substances	No Anti-A or Anti-B substances
2. --	--	No A or B substances	No Anti-A or Anti-B substances
3. O-Rh+	Anti-A, Anti-B	No A or B substances	No Anti-A or Anti-B substances
4. O-Rh-	Anti-A, Anti-B	No A or B substances	Trace of Anti-A and Anti-B substances
5. O-Rh+	Anti-A, Anti-B	No A or B substances	Trace of Anti-A substance

Glucose.—

Most of the determinations in Table V indicate a lower concentration of glucose in maternal blood than in mole fluid. Similarly cord blood shows a lower glucose level than maternal blood. These findings suggest that the passage of glucose across immature and mature trophoblast is slow, and that the environment of the embryo and fetus is relatively low in glucose. It is

TABLE V. GLUCOSE CONTENT OF MATERNAL SERUM AND MOLE FLUID

	SERUM (MG./100 ML.)	MOLE FLUID (MG./100 ML.)
1.	76	62
2.	150	71
3.	113	63
4.	199	173
5.	111	52
6.	--	42
7.	120	134
8.	94	22
9.	103	24
10.	103	82
Average	118.7	72.5
Maximum	199	173
Minimum	76	22

of considerable interest to observe the lower glucose levels in the mole fluid even in the absence of embryonic tissue which would normally be utilizing the glucose and thus lowering the concentration in fetal blood.

Calcium, Inorganic Phosphate, Alkaline and Acid Phosphatase.—

From the average figures presented in Table VI it is apparent that mole fluid has a lower calcium content than the surrounding serum. This is divergent from the observations on cord blood which have usually shown a higher level of calcium than in maternal blood. Mull[24] found the calcium levels of fetal blood at term to average about 1.5 mg./100 ml. higher, and further that elevations in the maternal blood were reflected in elevations in fetal blood. Part of the explanation for this discrepancy between cord blood and mole fluid may be explained by the fact that mole fluid has such a relatively low total protein, and the decrease may well be due to a lower protein-bound calcium. Determinations of diffusible calcium have not been done, but in view of the low protein content of mole fluid it seems likely that the preponderance of mole fluid calcium is diffusible calcium. The calcium levels in mole fluid are comparable to the low levels in ascitic and edema fluid as demonstrated by Hastings.[12]

TABLE VI. CALCIUM, INORGANIC PHOSPHATE, ALKALINE AND ACID PHOSPHATASE

	CALCIUM (MG./100 ML.)		INORGANIC PHOSPHATE (MG./100 ML.)		ALKALINE PHOSPHATASE (BODANSKY UNITS)		ACID PHOSPHATASE (BODANSKY UNITS)	
	SERUM	MOLE FLUID	SERUM	MOLE FLUID	SERUM	MOLE FLUID	SERUM	MOLE FLUID
1.	- -	6.4	9.7	11.8	2.2	6.3	1.0	5.9
2.	9.3	9.5	6.7	16.1	2.1	4.4	- -	7.1
3.	- -	- -	6.8	- -	1.5	7.3	0.5	5.7
4.	- -	7.4	- -	- -	- -	3.4	- -	11.1
5.	- -	- -	5.9	12.3	5.0	7.4	0.2	7.0
6.	8.9	6.6	- -	- -	- -	- -	- -	- -
7.	- -	- -	5.3	7.8	2.4	21.8	0.0	8.4
Average	9.1	7.4	6.9	12.0	2.6	8.4	0.4	7.5
Maximum	9.3	9.5	9.7	16.1	5.0	21.8	1.0	11.1
Minimum	8.9	6.4	5.3	7.8	1.5	3.4	0.0	5.7
CALCIUM AND INORGANIC PHOSPHATE IN MILLIMOLES/LITER								
Average	2.27	1.85	2.23	3.89				
Maximum	2.32	2.37	3.14	5.20				
Minimum	2.22	1.60	1.71	2.52				

Like cord blood, mole fluid has a higher phosphate content than the maternal blood, but the level in mole fluid is proportionately higher. These findings suggest that both immature and mature trophoblast are able to concentrate phosphate on the "fetal side." The reason for this is not clear but the transfer of various metabolic products is probably associated with the process of phosphorylation, in addition to the fact that phosphate, as well as calcium, is needed in the formation of fetal bone.

Edema fluid and ascitic fluid differ from mole fluid in their phosphate contents in relation to serum. It has already been noted that the potassium level is relatively higher in mole fluid than in edema fluid. This same discrepancy was noted by Manery[20] in her study of rabbit tendon and it would appear that mole fluid resembles tendon fluid more closely than edema fluid in this respect. Manery explained the potassium and phosphate elevations on the basis of cell content, which she estimated as 10 per cent of the wet weight of tendon. This same explanation does not necessarily apply to mole fluid since the cells were discarded by centrifugation.

Alkaline phosphatase and acid phosphatase activity are two times and fourteen times as high in the fluid as in the surrounding serum. Cord-blood

alkaline phosphatase is also slightly higher than in maternal blood. It is of interest that it rises to a still higher level in the infant's blood in the immediate neonatal period.[32] The origin of these high phosphatase activities is not clear. It is noteworthy, however, that the normal early trophoblast, as well as molar trophoblast, exhibits high acid and alkaline phosphatase activity, and it may be that some is passed on to the fluid in the vesicles from this source.

Cholesterol.—

Fluid from three moles and their corresponding maternal sera were analyzed for cholesterol. The total and free cholesterol of the maternal sera was within normal limits, but none of the samples of mole fluid contained any cholesterol, which strongly suggests that this substance does not pass from the maternal to the fetal circulation. The tests were done on small volumes of fluid and therefore it is possible that trace amounts may traverse the placental barrier. The cholesterol levels of cord blood are consistently lower than those of maternal blood,[26] and from the studies reported herein it seems likely that the major portion of cholesterol in cord blood is synthesized by the fetus itself.

Ascorbic Acid.—

Two ascorbic acid determinations revealed levels of 0.44 mg./100 ml. and 1.38 mg./100 ml. in the maternal serum, with 0.713 mg./100 ml. and 1.09 mg./100 ml. in the respective mole fluids. The determinations are too few to draw any conclusions from, except that there does not appear to be any major difference in the concentration of ascorbic acid in serum and in mole fluid. Fetal cord blood has been demonstrated to have a higher ascorbic acid content than maternal blood.[32, 26]

Iron.—

While the "available" iron content of serum and mole fluid varies greatly from one specimen to the next, there is a rather constant two-to-one ratio between serum and mole-fluid iron (Table VII). This relationship appears to be the reverse of that found in maternal blood and fetal blood at term, when the serum iron of maternal blood averages 80 μg/100 ml. and the fetal-serum iron averages 150 μg/100 ml. According to Smith,[32] the relatively low iron content and higher iron-binding capacity of maternal serum indicate that there is a movement of iron from storage into hemoglobin. The reverse situation is found in the fetal serum suggesting iron storage. In the hydatidiform-mole fluid the relatively low iron content, compared with the maternal serum, might merely be related to the fact that there is no hemoglobin synthesis (in the absence of an embryo) and hence no storage of iron takes place.

TABLE VII. SOLUBLE IRON CONTENT OF SERUM AND MOLE FLUID

CASE	SERUM IRON (μG/100 ML.)	MOLE FLUID IRON (μG/100 ML.)
1.	160	70
2.	255	150
3.	70	30
4.	15	5
5.	200	97

Summary and Conclusions

The fluid from the vesicles of hydatidiform moles has been analyzed for the following chemical constituents: sodium, chloride, potassium, total protein, total solutes, carbon dioxide content, oxygen content, nonprotein nitrogen, uric acid, creatinine, amino acid nitrogen, protein-bound iodine, glucose, ABO blood group antigens and agglutinins, calcium, phosphate, alkaline and acid

phosphatase, cholesterol, ascorbic acid, and iron. The concentration of these substances has been briefly compared with those in the maternal blood, cord blood, ascitic and edema fluid, and tendon.

TABLE VIII*

	SERUM	ASCITIC FLUID	EDEMA FLUID
Water	GM./C.C. 0.924	GM./C.C. 0.964	GM./C.C. 0.988
Total protein	GM./KG. H_2O 66.2	GM./KG. H_2O 27.6	GM./KG. H_2O 3.00
	MM/KG. H_2O	MM/KG. H_2O	MM/KG. H_2O
Total carbon dioxide	30.8	31.8	31.8
Bicarbonate	29.3	30.2	30.4
Chloride	118.8	118.0	120.0
Phosphate	1.3	1.2	1.2
Sodium	166.8	155.0	156.2
Potassium	6.0	- -	4.1
Calcium	2.8	2.0	1.6

*Taken from Hastings et al.[13]

It is suggested that: (1) Mole fluid is an interstitial fluid and is essentially similar in composition to other environmental fluids such as ascitic and edema fluid and that of normal tendon. (2) Water is retained on the "fetal side" of the early trophoblast against the force of a higher osmotic pressure in the surrounding maternal serum. (3) The primitive trophoblast of moles concentrates amino acids on the "fetal side" and may allow the passage of small amounts of normal serum albumin. (4) Protein-bound iodine, presumably thyroxin, crosses the early trophoblastic barrier. (5) Cholesterol does not cross the early trophoblast, at least in concentrations high enough to be detected by the Sperry-Schoenheimer technique. (6) Glucose passes through the early trophoblast at a slow rate.

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STUDIES OF THE FUNCTION OF EARLY HUMAN TROPHOBLAST

II. Preliminary Observations on Certain Chemical Constituents of Chorionic and Early Amniotic Fluid*

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THE first few days of embryonic life are spent in the immediate environment of a gelatinous matrix called the magma reticularis. In time a small cavity appears in the magma, to one side of the primitive ectoderm, which is filled with fluid and which is referred to as the extraembryonic celom or chorionic cavity (Figs. 1 and 2). The amniotic cavity at this early stage of development is very small in relation to the size of the chorionic cavity. The amniotic chamber, however, progressively increases in size so that the chorionic cavity by the ninth week of pregnancy is relatively small (Fig. 3), and at term is completely obliterated. While the chorionic cavity is being displaced, the embryo more and more derives its nutrition from the chorion frondosum ("placental villi") by way of the body stalk and chorionic vessels. Prior to the fifth gestational or third developmental week, however, when the embryonic-villous circulation is established, the embryo derives all its nutrient materials from the connective-tissue fluid of the chorionic cavity. This fluid is assumed to be the product of the trophoblast and of the primitive mesenchymal cells of the gelatinous inner shell which control its chemical composition.

With these facts and assumptions in mind, it was thought that knowledge of the composition of chorionic fluid might yield some evidence as to the nature of the function of the primitive trophoblast, and the nature of the environment of the early embryo. It was also thought that a similar study of the amniotic fluid might lead to knowledge of the mechanisms involved in the differential expansions of the chorionic and amniotic cavities in these early stages of development.

It is the purpose of this report to present some observations on certain chemical constituents of these fluids in early ovisacs. Primary attention has been focused on substances responsible for osmotic activity, since it was thought that protein and electrolyte changes might be responsible for the reciprocal accumulation of fluid in these two chambers at different periods of embryonic life.

This must necessarily be a preliminary and fragmentary report because of the scarcity of material for analysis.

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Materials and Methods

The materials in this study consisted of intact ovisacs obtained at the time of hysterotomy or hysterectomy. The operations were performed for such indications as tuberculosis, chronic nephritis, and diabetes. After the ovisac was measured, a needle was inserted into the chorionic cavity and the fluid aspirated. In the case of the 7.5 cm. embryos, the fluid, because of its viscous nature, could not be aspirated through the needle but consisted of a gelatinous material (magma reticularis) which was cut and placed in a tube. On

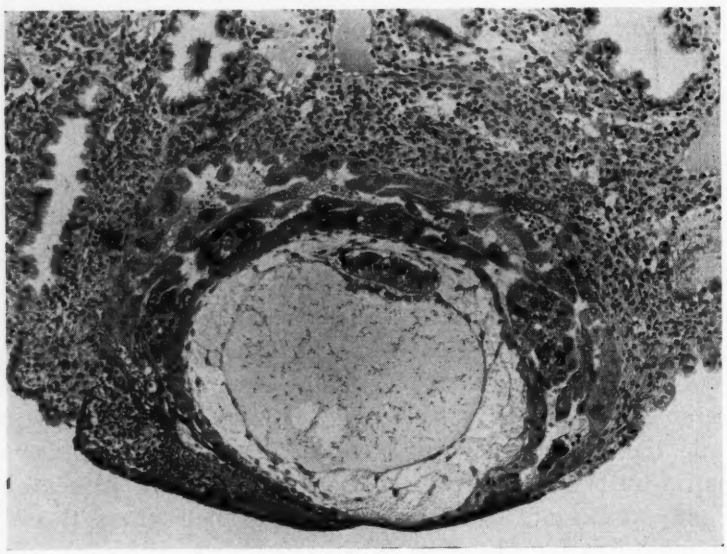

Fig. 1.—Photomicrograph of 12½ day ovum. Carnegie ovum 7700. Same specimen as shown in Fig. 2. (Taken from Hertig and Rock.[1]) (×100; reduced ⅕.)

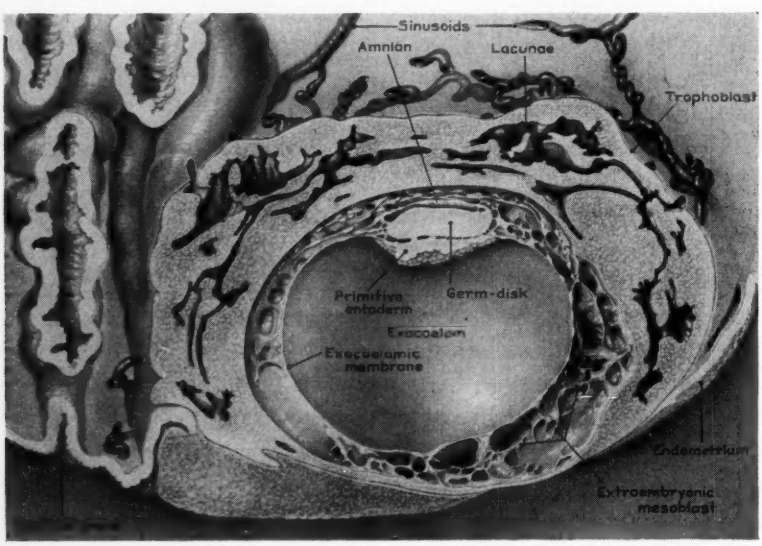

Fig. 2.—Reconstruction of 12½ day ovum. The amniotic chamber at this stage is small but in time progressively surrounds the embryo and eventually expands to obliterate the chorionic cavity (exocelom). Carnegie ovum 7700. Same specimen as shown in Fig. 1. (Taken from Hertig and Rock.[1])

centrifugation the gel changed to a sol which constituted the material for analysis. In the case of the 16.3 cm. fetus the chorionic cavity was completely obliterated and only amniotic fluid could be obtained. After aspiration of chorionic fluid in the majority of specimens, a needle was inserted into the amniotic cavity and its fluid aspirated. The amounts of both of these fluids varied a great deal. In conformity with the changing anatomical relationships, when amniotic fluid was abundant chorionic fluid was scant, and the actual amounts varied from 1 to 5 ml. of chorionic fluid and 5 to 100 ml. of amniotic fluid.

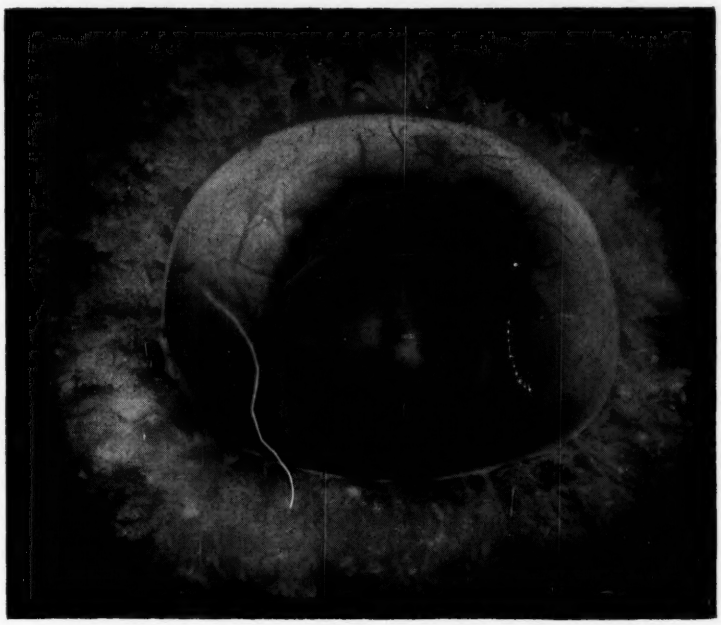

Fig. 3.—A 9 week human ovum showing the embryo immediately encased in its filmy amnion. The space between the amnion and the thick chorionic shell contains the magma reticularis. The small globular structure lying between the amnion and chorion near the tail region is the yolk sac. (Photograph through the courtesy of Dr. George Corner of the Carnegie Institution. Carnegie ovum No. 7A.)

The specimens were centrifuged and the supernatant was decanted. This was frozen with the use of dry ice and stored in the frozen state in tightly stoppered tubes for subsequent analysis. Because of the often small amounts of fluid involved, not all the determinations could be made on all the samples. The concentrations of the following substances were determined: sodium, potassium, chloride, total protein, glucose, inorganic phosphate, alkaline and acid phosphatase, and cholesterol. In one case only a carbon dioxide content; a bicarbonate content; a pH determination, and a freezing-point depression determination were done on chorionic fluid. The methods used have been the same as those reported in the previous study on the fluid of hydatidiform moles.[3]

Results and Comment

Chorionic Fluid.—

While the average values presented in Tables I and II must remain tentative because of the small number of samples tested, some interim conclusions may be permissible. In general, the chemical composition of chorionic fluid resembles that of mole fluid in its relation to the composition of maternal serum. Average concentrations of sodium, chloride, total protein, and glucose

TABLE I. CHORIONIC FLUID

LENGTH OF EMBRYO	APPROXIMATE MENSTRUAL AGE	SODIUM (MEQ. PER LITER)	POTASSIUM (MEQ. PER LITER)	CHLORIDE (MEQ. PER LITER)	TOTAL PROTEIN (GM./100 ML.)	GLUCOSE (MG./100 ML.)	INORGANIC PHOSPHATE (MG./100 ML.)	ALKALINE PHOSPHATASE (BODANSKY UNITS)	ACID PHOSPHATASE (BODANSKY UNITS)
7 mm.	6 weeks	137	—	101	—	100	—	—	—
7 mm.	6 weeks	142	—	115	0.450	—	—	—	—
2.3 cm.	8 weeks	104	5.2	—	1.02	—	8.26	0.00	0.00
2.5 cm.	8 weeks	134	5.4	—	—	86	12.9	12.1	—
2.6 cm.	8 weeks	—	—	—	—	—	6.85	6.64	6.49
2.9 cm.	8½ weeks	137	6.2	105	0.400	81	—	—	—
2.9 cm.	8½ weeks	134	4.6	128.8	—	—	—	—	—
6.0 cm.	9½ weeks	136	5.8	86.7	0.775	—	—	—	—
7.5 cm.	13 weeks	—	—	—	—	—	—	—	—
7.5 cm.	13 weeks Magma reticularis	134	4.6	142	1.02	—	8.25	0.67	1.19
16.3 cm.	20 weeks	—	—	—	—	—	—	—	—
Average		132.2	5.3	113.2	0.733	89	9.06	4.85	2.56
Maximum		142	6.2	142	1.02	100	12.9	12.1	6.49
Minimum		104	4.6	86.7	0.400	81	6.85	0.00	0.00

TABLE II. AMNIOTIC FLUID

LENGTH OF EMBRYO	APPROXIMATE MENSTRUAL AGE	SODIUM (MEQ. PER LITER)	POTASSIUM (MEQ. PER LITER	CHLORIDE (MEQ. PER LITER)	TOTAL PROTEIN (GM./100 ML.)	GLUCOSE (MG./100 ML.)	INORGANIC PHOSPHATE (MG./100 ML.)	ALKALINE PHOSPHATASE (BODANSKY UNITS)	ACID PHOSPHATASE (BODANSKY UNITS)
7 mm.	6 weeks	—	—	—	—	—	—	—	—
7 mm.	6 weeks	—	—	—	—	—	—	—	—
2.3 cm.	8 weeks	142	—	—	—	—	—	—	—
2.5 cm.	8 weeks	124	4.8	—	—	99.5	11.7	3.1	1.65
2.6 cm.	8 weeks	—	—	—	—	—	—	—	—
2.9 cm.	8½ weeks	155	4.7	133	—	53	8.6	7.1	4.9
2.9 cm.	8½ weeks	74	4.7	—	—	—	—	—	—
6.0 cm.	9½ weeks	84	2.6	80.8	0.260	—	14.9	7.3	2.4
7.5 cm.	13 weeks	103	5.4	108	—	—	—	—	—
7.5 cm.	13 weeks	165	4.9	—	0.44	—	4.73	3.41	3.86
16.3 cm.	20 weeks	120	3.3	92	—	—	2.93	4.89	4.76
Average		120.8	4.34	103.4	0.350	76.2	8.57	5.1	3.51
Maximum		165	5.4	133	0.440	99.5	14.9	7.3	4.9
Minimum		74	2.6	80.8	0.260	53	2.93	3.41	1.65

are all lower than average levels of these materials in maternal serum. At the same time, potassium, inorganic phosphate, and alkaline and acid phosphatase are more concentrated in chorionic fluid than in maternal serum. The absence of a measurable amount of cholesterol in chorionic fluid is in agreement with the studies on mole fluid. It is therefore suggested that the normal trophoblast of the chorionic vesicle of the early ovisac functions in a qualitatively similar manner to that of the hydatidiform mole vesicle. The conclusions drawn in the previous paper appear to apply not only to molar trophoblast but to the normal early trophoblast as well.

While these divergences in concentrations of certain constituents are in the same direction as those of mole fluid, the differences from maternal serum are less marked than those in mole fluid. Except for cholesterol and total protein, the concentrations of all the substances measured approached the concentration in serum, and arranged themselves in an intermediate zone. The explanation for the quantitative differences is not apparent. The presence of metabolically active embryonic tissue in chorionic fluid may be significant. It is possible that these differences may be related to the fact that the trophoblast of the hydatidiform mole is a potentially malignant tissue which perhaps behaves qualitatively the same as its normal counterpart but quantitatively in a different way. Histologically, molar trophoblast tends to be undifferentiated and recapitulates the very early stages of chorionic development. Therefore, its presumably more primitive function may be maintained in a state of "suspended animation." Thus, the fluid from moles might not be strictly comparable to the chorionic fluid in the normal specimens examined, inasmuch as the latter are the products of a more mature trophoblast.

Single determinations on the chorionic fluid of an ovisac with a 2.9 cm. embryo revealed a pH of 7.45, a carbon dioxide content of 24.2 milliequivalents per liter and a bicarbonate of 23.4 milliequivalents per liter.

One interesting property of the gelatinous material of the chorionic cavity is the ease with which it can be changed from a gel to a sol. A slight pressure on the gel or slow centrifugation are all that appear to be required to convert it to a nonviscous fluid. This observation seems to classify this material (magma reticularis) as a thixotropic gel. This property of the magma might explain in part the apparent ease with which the diaphanous and flimsy amniotic membrane of early gestation expands against, and eventually obliterates, the chorionic chamber.

Amniotic Fluid of Early Pregnancy.—

The remarkably wide variations in the sodium concentrations, as shown in Table II, suggest that, at least in the early stages of development, this fluid is much less constant in its composition than its contemporary chorionic fluid. In three instances the sodium level in amniotic fluid was 18 to 38 milliequivalents higher than the level in the corresponding chorionic fluid, and in three instances it was 10 to 52 milliequivalents lower. The average sodium concentration was lower than that of maternal serum, chorionic fluid, or even mole fluid.

The chloride concentrations fluctuated to almost the same degree as the sodium and varied directly with the sodium. The average concentration of chloride was likewise lower in amniotic fluid than in serum, chorionic fluid, or mole fluid.

The potassium content was less variable and was on an average lower in amniotic fluid than in the other fluids examined. The concentrations of potassium were very similar to those of normal serum. The total protein content of amniotic fluid was lowest of all the various fluids examined, and compared reasonably well with the determinations of Makepeace[2] (Table III).

TABLE III. COMPARISON OF PRESENT DATA WITH THOSE OF MAKEPEACE

	AVERAGE CONCENTRATIONS		SERUM AVERAGE CONCENTRATIONS		AMNOITIC FLUID (FIRST 4 MONTHS OF GESTATION) AVERAGE CONCENTRATIONS	
	MOLE FLUID	CHORIONIC FLUID	PRESENT SERIES	MAKEPEACE SERIES*	PRESENT SERIES	MAKEPEACE SERIES*
Sodium	123.4 meq./L.	132.2 meq./L.	136.9 meq./L.	133 meq./L.	120.8 meq./L.	131.1 meq./L.
Potassium	6.7 meq./L.	5.3 meq./L.	5.0 meq./L.	----	4.34 meq./L.	----
Chloride	107.6 meq./L.	113.2 meq./L.	115 meq./L.	104 meq./L.	103.4 meq./L.	110 meq./L.
Total protein	1.07 Gm./ 100 ml.	0.733 Gm./ 100 ml.	6.15 Gm./ 100 ml.	6.0 Gm./100 ml.	0.350 Gm./ 100 ml.	0.238 Gm./ 100 ml.
Glucose	72.5 mg./ 100 ml.	89 mg./100 ml.	118.7 mg./ 100 ml.	118 mg./ 100 ml.	76.2 mg./ 100 ml.	57 mg./ 100 ml.
Inorganic phosphate	13.4 mg./ 100 ml.	9.06 mg./ 100 ml.	7.29 mg./ 100 ml.	----	8.57 mg./ 100 ml.	----
Alkaline phosphatase	8.43 Bodansky units	4.84 Bodansky units	2.64 Bodansky units	----	5.1 Bodansky units	----
Acid phosphatase	7.54 Bodansky units	2.56 Bodansky units	.44 Bodansky units	----	3.51 Bodansky units	----
Osmoles per liter	.254 osmoles/L.	----	.275 osmoles/L.	.299 osmoles/L.	----	.291 osmoles/L.
Total cholesterol	0.00 mg./ 100 ml.	0.00 mg./ 100 ml.	----	----	0.00 mg./ 100 ml.	----

*These concentrations were calculated from the cases in Makepeace's series from the second to the fourth month of gestation.

Although freezing-point depression determinations were not done, the observations on eletctrolyte and protein concentration of this early amniotic fluid suggest that it has a lower osmotic pressure than serum, and that this condition exists at a time in the development of the ovum when the amniotic chamber is expanding and displacing the chorionic cavity. Not only is this osmotic activity lower than that of serum, but it is also lower than that of the fluid of the chorionic cavity which is becoming obliterated. Makepeace's freezing-point depression observations on amniotic fluid in the *later months* of gestation demonstrated a similar low osmotic activity of amniotic fluid. These findings suggest that, in the formation of amniotic fluid, water is transferred to, or retained in, the amniotic cavity in spite of higher osmotic pressures in the surrounding serum and chorionic fluids. The production of mole fluid and chorionic fluid seems to take place in a similar manner. There appears to be an "osmotic gradient" in which the serum has the highest osmotic concentration, the chorionic fluid occupies an intermediate position and the amniotic fluid has the lowest osmotic activity. Obviously this idea needs further testing and is actually at odds with the observations of Makepeace on the freezing-point depressions of amniotic fluid from ovisacs in the first four months of gestation, which he found to have an osmotic activity slightly lower but almost the same as that of maternal serum.

The phosphate content and alkaline phosphatase activity are very similar to those of maternal serum which are lower than those of chorionic or mole fluid. The acid phosphatase activity is higher than that of serum but still lower than that of chorionic or mole fluid. The origin of this phosphatase is not apparent, but diffusion from either the trophoblast or embryonic tissue could explain it. Early trophoblast exhibits a relatively high acid phosphatase activity.

The glucose level is lower in amniotic fluid than in serum or chorionic fluid, and there appears to be a gradient with the highest levels in serum, intermediate levels in chorionic fluid, and the lowest concentration in the amniotic fluid. The glucose concentration appears to vary inversely with the water content.

Summary and Conclusions

Chorionic and amniotic fluid from ovisacs of the first few months of pregnancy have been analyzed for their sodium, potassium, chloride, total protein, glucose, inorganic phosphate, acid and alkaline phosphatase, and cholesterol content. These measurements suggest that:

1. When compared with maternal serum, chorionic fluid resembles mole fluid in its composition, inasmuch as it contains a lower concentration of sodium, chloride, total protein and glucose, and a higher concentration of potassium, inorganic phosphate, and alkaline and acid phosphatase. Neither fluid contains measurable amounts of cholesterol.

2. The quantitative differences that exist between these two fluids may be due to differences in the function of potentially neoplastic trophoblast of the mole in contrast to the function of its normal homologous tissue.

3. There appears to be an "osmotic gradient" in which the osmotic activity of serum is greater than the osmotic activity of chorionic fluid, which in turn is greater than that of amniotic fluid.

4. Water appears to be concentrated in the chorionic and amniotic chambers in spite of a higher osmotic pressure in the environmental fluid, the maternal serum.

5. The glucose concentration of these three fluids varies inversely with the water concentration.

6. The magma reticularis appears to be a thixotropic gel.

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PERSISTENT TRANSVERSE PRESENTATION OF THE FETUS

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(From the Margaret Hague Maternity Hospital)

THIS is an analysis of cases of persistent transverse presentation of the fetus which occurred at the Margaret Hague Maternity Hospital between July 1, 1943, and June 30, 1952. In this nine-year period there were 72,482 live births with 86 of these termed persistent transverse presentations, making an incidence of 1:843. This series does not include any multiple pregnancies or any fetus that weighed under 1,500 grams. No oblique lie of the fetus is included.

Miscellaneous Statistics

Of the 86 patients, 56.9 per cent were over 30 years of age and 9.3 per cent were over the age of 40. There was one patient who was under 21 years of age.

In regard to parity 16.2 per cent were nulliparous and 83.8 per cent were multiparous, with 29 per cent of all patients at least para iv.

The length of gestation was between 30 and 36 weeks in 26, for 31 per cent, of the patients and over 36 weeks in 69 per cent.

There were 11 patients in whom labor was induced. In 7 of these the reason was complication factors and in the remaining 4 cases no reason was stated for the induction.

Fifty-four and nine-tenths per cent were admitted in labor; 17.4 per cent were admitted because of premature ruptured membranes; 17.4 per cent because of vaginal bleeding; and the remaining 10.3 per cent for other reasons.

Forty-two, or 48.8 per cent, of the cases were recognized as transverse lie on admission and 44, or 51.2 per cent, were not recognized until either some hours after admission or at actual delivery.

There were twelve x-rays taken to determine position. At the time of delivery the presentation was right scapular anterior in 29 patients, left scapular anterior in 22 patients, right scapular posterior in 7 patients, and left scapular posterior in 10 patients; no mention of presentation was made in the remaining 18. There were 36 vaginal examinations done for position.

Duration of Labor and of Ruptured Membranes.—

The hours of labor are shown in Table I.

TABLE I. DURATION OF LABOR

HOURS OF LABOR	NO. OF PATIENTS	PER CENT
0	8	9.3
1-12	61	70.9
13-24	12	14.0
24+	5	5.8

The longest case was seventy-six hours of labor before delivery was accomplished by decapitation.

The hours of ruptured membranes are shown in Table II.

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TABLE II. DURATION OF RUPTURED MEMBRANES

HOURS OF RUPTURED MEMBRANES	NO. OF PATIENTS	PER CENT
0	31	36.0
1-12	27	32.5
13-24	12	12.9
24+	16	18.6

The longest case of ruptured membranes was eight days. Five patients had premature ruptured membranes; 5 patients had prolonged ruptured membranes; 26 patients had premature and prolonged ruptured membranes.

Method of Delivery.—

The type of delivery is shown in Table III.

TABLE III. METHOD OF DELIVERY

	PATIENTS	PER CENT
1. Internal podalic version and extraction	41	48.2
2. Braxton Hicks version	16	18.6
3. Low transverse cervical cesarean section	16	18.6
4. Extraperitoneal cesarean section	5	5.8
5. Spontaneous (conduplicato corpore)	2	2.2
6. Decapitation	2	2.2
7. External cephalic version, forceps delivery	1	1.1
8. Internal cephalic version, Willets forceps	1	1.1
9. Spontaneous conversion, spontaneous delivery	1	1.1
10. Spontaneous conversion to breech, extraction and craniotomy	1	1.1

The spontaneous conversions listed in Table III were included because they occurred after the diagnosis was definitely made and at least eight hours of labor had ensued.

There were no maternal deaths.

Fetal and Neonatal Results.—

The weights of the infants are recorded in Table IV.

TABLE IV. WEIGHTS OF INFANTS

WEIGHT IN GRAMS	NO. OF INFANTS	PER CENT
1,500-2,500	25	29.0
2,600-3,500	40	46.7
3,600-4,000	14	16.2
4,000	7	8.1

There were 3 antepartum fetal deaths, 25 intrapartum and 9 neonatal deaths; of the 49 living children one had Erb's palsy and a fractured clavicle. The total fetal mortality was 43 per cent.

As previously mentioned, 48.8 per cent of the cases were recognized and in this group the fetal mortality was 30.9 per cent, as compared to a fetal mortality of 54.7 per cent in the group that was not recognized at or soon after admission. The fetal mortality in the recognized premature group was 50 per cent and in the-not-recognized premature group it was 58.8 per cent. The fetal mortality in the recognized cases in full-term infants was 26.4 per cent in contrast to 51.9 per cent infant mortality in the unrecognized term group.

In the recognized premature group there was a total of 8 babies with 2 delivered by cesarean section and 6 delivered by internal podalic version and extraction. Four infants in this group died, all delivered by version and extraction, 3 of the deaths were intra partum and one neonatal.

In the not-recognized premature group there was a total of 17 infants with 5 delivered by cesarean section; 8 delivered by version and extraction; 3 delivered by Braxton Hicks version; and one delivered conduplicato corpore. There were 10 deaths in this group, 7 intra partum, 2 neonatal, and one ante partum. One of the infants that died intra partum was delivered by cesarean section, 2 were delivered by internal podalic version and extraction, 3 were delivered by Braxton Hicks version; and the last was delivered conduplicato corpore. The 2 infants that died neonatally were both delivered by version and extraction as was the one that died ante partum.

There was a total of 34 full-term infants in the recognized group of cases, with 9 deaths. These deaths were one ante partum, 2 neonatal, and 6 intra partum. There were 11 cesarean sections with no infant deaths.

The not-recognized full-term group had a total of 27 infants with 13 deaths. These deaths were one ante partum, 3 neonatal, and 9 intra partum. There was 3 cesarean sections with one resulting in an intrapartum fetal death.

There were 21 cesarean sections, an incidence of 24.6 per cent; 16 of these were low transverse cervical and 5 were extraperitoneal. Nine were performed on nulliparous patients. There were 2 fetal deaths in the cesarean section cases, or 9.5 per cent. These 2 deaths were both in multiparous patients and both were intra partum, with one death known prior to surgery and the other suspected. Both were cases of neglected transverse lie and the reason for surgery was fear of rupturing a thin lower uterine segment with any intrauterine manipulation. Nine of these sections were done with the main indication of partial or central previa and one was done primarily for abruption of the placenta. There were 7 premature babies delivered by cesarean section with one death, and 14 full-term infants delivered by cesarean section, also with one death. The average weight of the babies delivered by cesarean section was 2,837 grams.

There were 41 internal podalic versions and extractions with a fetal mortality of 43.8 per cent. The infant mortality in the prematures of this group was 64.2 per cent and in the full-term, 33.3 per cent. There was one antepartum fetal death, 9 intrapartum, and 8 neonatal. The time for doing the version and extraction varied with the conditions present at the time the diagnosis of transverse lie was made. In the majority of cases, the version and extraction were done when the cervix was thought to be fully dilated and retracted. This was difficult to determine on rectal examination as the findings at vaginal examination proved. The next factor that determined intervention was prolapse of an arm or cord or both in a total of 19 cases. The version and extraction were done in 10 cases where the cervix was not fully dilated. The reason for immediate intervention was prolapse of cord or arm and the reason for extraction was fetal distress. The fetal mortality in these 10 cases was 50 per cent. The average weight of the babies delivered by version and extraction was 2,782 grams.

There were 16 patients in whom a Braxton Hicks version was done. The reason for version was prolapsed cord in one case; prolapsed arm in 3; prolapsed arm and cord in 2; and as the procedure of choice in the remaining 10 patients. The fetal mortality in this group was 62.5 per cent. There were 8 intrapartum deaths, one neonatal and one antepartum death. The time intervals between version and death of the fetus in the intrapartum deaths were: one fetus dead at time of version, one each after one hour, two hours, three hours, five hours, and six hours, and 2 after four hours. The neonatal death occurred 30 minutes after delivery and one hour after version. In the 10 cases in which the Braxton Hicks version was the procedure of choice the fetal mortality was 50 per cent. The average weight of the babies delivered by Braxton Hicks version was 3,082 grams.

There were 8 patients who were delivered by a procedure other than those previously discussed. Five of these were cases of neglected transverse lie; the remaining 3 cases were recognized early and followed to conclusion. Of these 3, there was one antepartum fetal death of an infant delivered conduplicato corpore, one case of external version with midforceps after prolapse of the cord occurred with resultant intrapartum fetal death; and, third, delivery of a living child after spontaneous conversion and breech delivery. This last patient was a para vii who had a pelvic x-ray series taken after eight hours of labor for disproportion and who delivered one hour later precipitously. The x-rays showed a transverse lie. The membranes were intact. The infant weighed 4,000 grams.

The fetal mortality in all vaginal deliveries, excluding the antepartum deaths, was 51.6 per cent and in cesarean section was 9.5 per cent.

There were 14 patients in whom the presentation was incorrectly diagnosed as breech and of these 14 there was a prolapse of the cord or arm in 8 cases. The infant mortality in these 14 cases was 71.5 per cent.

Complications in Transverse Presentation.—

The associated and resultant complications are listed in Table V.

TABLE V. COMPLICATIONS

COMPLICATION	NUMBER	PER CENT
Prolapsed cord	15	17.4
Prolapsed arm	25	29.0
Toxemia of pregnancy	12	13.6
Placenta previa	9	10.4
Abruptio placentae	6	6.8
Cervical laceration	3	3.4
Short cord	1	1.1
Diabetes mellitus	1	1.1
Ruptured uterus	2	2.2
Chronic inversion of uterus	1	1.1
Abdominal hysterectomy	2	2.2
Vaginal hysterectomy	1	1.1

One rupture of the uterus occurred after a version and extraction were done through an 8 cm. dilated cervix. The reason for version and extraction was prolapse of the cord with fetal distress. The baby had Erb's palsy and a fractured clavicle.

The other rupture of the uterus occurred after five hours of labor. The patient had an attempted external version followed by a Braxton Hicks version which was accomplished through a 6 cm. cervix. Spontaneous delivery occurred fifteen minutes later. There was vaginal bleeding post partum and shock occured one hour after delivery.

The vaginal hysterectomy was performed on the seventieth postpartum day because of chronic inversion of the uterus. This patient was delivered by decapitation of the fetus after seventy-six hours of labor.

Comment

It is felt that the treatment of choice in persistent transverse presentation is immediate cesarean section with two exceptions. One is antepartum fetal death and the other is the presence of a fully dilated cervix as determined by vaginal examination in the operating room prior to surgery. There are some cases that are going to be on the border line as to full dilatation and it is in these cases that experience and the individual condition of the uterus, membranes, fetus, and patient as a whole must be carefully considered and evaluated.

For those who favor careful observation of an early recognized transverse lie through hours of labor with the intent of a successful vaginal delivery, we reviewed the 65 cases of vaginal delivery and found 19 cases that we believe met the ideal conditions for a successful vaginal delivery. These 19 cases were recognized early and progressed to full dilatation before intervention. The fetal mortality in this group was 10 infants, or 52.6 per cent. Prolapse of the cord occurred in 4 cases with only one infant living. In all these cases in which vaginal delivery is awaited, the factor to fear most is prolapse of either the arm or the umbilical cord. There is no way in which this can be anticipated prior to its occurrence and no way in which it can be prevented. When it did occur, even though delivery was accomplished as soon as possible after prolapse, the fetal mortality in these cases was still five and one-half times as great as when the case was terminated by cesarean section. There were 2 cases of prolapse of the cord with delivery of a normal, living child by cesarean section. In both these cases the prolapsed cord and the presenting part were held out of the pelvis by the examining hand until delivery was accomplished.

The average weight of the infants born by cesarean section was less than that of those delivered by version and extraction or by Braxton Hicks version. The three smallest babies delivered by cesarean section weighed 1,500, 1,510, and 1,790 grams; all these babies lived. The improvement in operative technique, anesthesia, and pediatric care invalidates the argument against section in this group.

The thought that vaginal delivery would be easier with a premature infant because the infant is smaller and therefore more maneuverable is not true. The fetal mortality in premature infants delivered by the vaginal route was 72.2 per cent. In this group there were 14 patients delivered by version and extraction, 3 by Braxton Hicks version, and one spontaneously conduplicato corpore.

One cannot stress too much the importance of a careful examination on admission of the patient to the delivery floor. Of the 86 cases, 51.2 per cent were not recognized on admission nor within a reasonably short time thereafter. The shortest length of time a patient was on the delivery floor before death of the fetus occurred was three hours; this happened in 2 cases. There was one patient on the delivery floor four hours before fetal death occurred and in all other cases the time was five hours or more, with the longest time sixty hours.

Though we did not have a maternal death, the fact that 3 uteri were sacrificed as a direct result of a transverse lie is disaster enough. The incidence of hysterectomy in this group was 3.3 per cent, and the 3 patients involved might easily have died. We have stressed the increased fetal survival throughout this paper, but we also wish to place equal importance on the loss of uteri and possible maternal deaths in institutions not having access to immediate blood replacement and immediate surgery.

It has been mentioned that diagnoses of breech presentation were made in 14 of these cases. We now do a vaginal examination on all patients suspected of having a footling breech to confirm the diagnosis and in any suspected breech presentations where the diagnosis is uncertain.

Conclusions

1. Eighty-six cases of persistent transverse lie and their management are presented.

2. Immediate cesarean section is advised as the procedure of choice with two exceptions given.

3. The fetal mortality in vaginal deliveries was 5.6 times as great as that in cesarean section. The fetal mortality is discussed from the standpoint of recognition, prematurity, and type of delivery.

4. There were no maternal deaths.

5. The complications of transverse lie are presented with regard to prevention and management.

EMOTIONAL ILLNESS ASSOCIATED WITH CHILDBIRTH

A Study of 52 Patients and the Literature

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ORDINARILY the arrival of a new baby is a joyful time, the culmination of much pleasurable anticipation and planning on the part of the parents, grandparents, and friends. Too often this happiness is shattered by the tragic appearance of severe emotional illness in the new mother. Depression and anxiety replace happiness, bringing confusion, disorganization, and even tragedy in its stead.

How often does this illness strike? A number of students of the problem have reported figures indicating an incidence of one psychosis in every four hundred confinements. In surveys of large numbers of women admitted to mental hospitals it appears that about 8 per cent of such admissions are due to psychosis following childbirth. In this study, which was made in a private sanitarium, 13.2 per cent of new female admissions to the hospital in the year 1951 were women with postpartum emotional illness. Unfortunately, such figures underestimate the true incidence of such disorders. Many women who become emotionally ill following childbirth never reach the mental hospital to become part of its statistical tables. Many of these women struggle through their illness at home, some attaining spontaneous recovery, others remaining chronically handicapped by emotional illness. Many others are treated by their family doctors, by obstetricians, or by psychiatrists in private practice.

One can only speculate on the true incidence of these disorders. Certainly, it seems to be conservative to place the figure at double that shown by the mental hospital studies. If one includes the many women in whom milder, yet incapacitating, forms of emotional illness appear, the estimate would have to be placed even higher. It seems fair to presume that about 5 per cent of women who become pregnant will have some form of emotional illness following the birth of one of their children.

Piker[1] from a review of the literature and his own studies, determined the following significant fact: Of all females who suffer from psychoses of various sorts, almost 9 per cent develop their mental disorders in connection with the reproductive period. He comments: "That 9 per cent, it seems to me, places a problem squarely in the laps of obstetricians. Since an appreciable proportion of the psychotic female population develops its mental disturbance while under the observation of the obstetrician, he owes it to his patients and to the cause of medical progress generally to examine this problem carefully, and to take whatever steps he can toward diminishing its seriousness."

Relation of Pregnancy to Type of Psychosis

Early observers attempted to establish the postpartum psychoses as specific diseases. It is now known that these emotional illnesses are the same in all respects as emotional illnesses occurring apart from pregnancy. Pregnancy and childbirth do not cause the illness, but rather serve as precipitating factors.

Pregnancy and childbirth, particularly childbirth, precipitate an array of emotional reactions ranging from relatively mild anxiety states to severe schizophrenic reactions. Various writers on the subject have indicated their respective findings in regard to the incidence of the various specific types of reactions. Brew and Seidenberg[2] reported 51.8 per cent schizophrenic reactions and 42 per cent manic-depressive. Of the schizophrenic reactions, 57 per cent were indicated to be catatonic and 26 per cent paranoid. Boyd,[3] in an extensive study of the literature, found that the reported distribution was as follows: manic-depressive, 40 per cent, schizophrenic reactions, 20 per cent, delirium, 28.5 per cent, psychoneurosis, 6 per cent, and psychosis with psychopathic personality, 5 per cent. Other reports indicate a varied distribution of diagnostic types.

In this study of 52 hospitalized patients the distribution was as follows: 75 per cent schizophrenic reactions, 11.5 per cent depressive reactions, and 13.5 per cent psychoneurotic reactions.

It is my impression that the majority of *severe* postpartum emotional illnesses are schizophrenic in nature, although the symptoms may be such that only close study will reveal the schizophrenic nature of the process. These illnesses often present a considerable amount of affective involvement, usually depressive in nature. Undoubtedly some observers have classified these depressed patients as having manic-depressive reactions, overlooking the basic schizophrenic components of the illness. Accurate diagnosis is important from the standpoint of treatment and of prognosis.

Time of Appearance in Relation to Pregnancy

When are these emotional illnesses associated with pregnancy most likely to become manifest? Boyd's study indicated that 14 per cent occur during pregnancy, 54 per cent during the early puerperal period (first 14 days post partum), and that 32 per cent occur during the late puerperal period. Piker,[1] on the basis of a survey of 770 cases reported in the literature, found that 24 per cent had their onset during the pregnancy and 76 per cent occurred post partum. Of the latter group, 80 per cent occurred during the first two weeks and only 4 per cent during the lactation period.

In this group of 52 cases 13 per cent had their onset during pregnancy, 25 per cent within one week following delivery, 13 per cent during the second, third, and fourth weeks following delivery, and the other 49 per cent occurred later than one month following delivery. The onset was considered to be acute in 20 per cent and gradual in 80 per cent of the patients.

My experience is in accord with Zilboorg's,[4] that the depressions, combined with marked suicidal and infanticidal impulses, develop acutely and are obvious to the patient's relatives and friends; the neuroses are slower in developing; the schizophrenias are likely to be the slowest and the most insidious in development.

Some writers feel that a time limit should be established in assigning the onset of emotional illness to a pregnancy experience. This seems impractical and unscientific because the onset of illness may be insidious and various factors may contribute to the slow development of symptomatic reactions. It is more desirable to evaluate patients individually to determine the relationship between illness and a pregnancy. Zilboorg stressed that the development of the post-

partum schizophrenias is very slow, at times extremely insidious, and as a result of this the etiological relationship between childbirth and the psychosis is not infrequently overcast by a number of intervening factors and thus overlooked. He expressed the opinion that the acute phase usually sets in within the first 6 to 10 months after childbirth.

Other specific factors which have been evaluated in considering the onset of these particular illnesses have been: the age of the patient, the length of time married, and the parity of the patient. From various figures reported and from a study of the age distribution in the present group of patients, it appears that there is nothing of statistical significance in regard to age distribution, in regard to the number of years married, or to the age at which marriage occurred. In regard to the parity of the patients, most writers have felt that these illnesses were more likely to occur after the first or second pregnancy, and particularly after the second. Some, however, have pointed out that the normal distribution of pregnancies has not been taken into account in formulating such conclusions and that, therefore, the incidence relating to parity is not of statistical significance.

In the 52 patients studied here the distribution was equal for para i, iii, and iv—ten each. Nineteen developed their illness following the birth of the second child, two following the fifth, and one following the seventh. Sixteen of these patients, however, had had a severe emotional illness following previous pregnancies and nine of the group had had mild emotional illness following previous pregnancies. These facts change the significance of the figures considerably. When these previous episodes of illness are considered, it is evident that almost all of these patients had their initial illness following the birth of the first or second child.

Although the figures are not statistically valid, they lend strength to the impression that the illnesses are more likely to make their initial appearance after the first or second pregnancy. The psychopathological factors involved in these illnesses are such that one would anticipate the appearance of symptoms following an early pregnancy.

Predisposing Factors

In view of the fact that these emotional illnesses are not peculiar to the pregnant or postpartum state, one can anticipate that the predisposing factors will be the same as for emotional illnesses in general.

This detailed study of 52 women suffering from postpartum emotional illness reveals several important predisposing factors. These appear frequently enough to give them possible significance in evaluating an individual woman's potentiality for developing an emotional illness associated with pregnancy. If one could detect this potentiality for illness in the individual, the institution of appropriate treatment might prevent some of the illnesses from becoming overt.

1. Attitude Toward the Pregnancy.—In this series of patients the attitude was good in 5, mixed in 39, and bad in 8. The woman's initially expressed attitude toward the pregnancy is not necessarily her real attitude.

Menninger[5] summarized this very neatly in the following words: "From investigations into the unconscious we have learned that an individual may consciously express one attitude, wish or intention, while he unconsciously harbors an entirely different or even opposite one. Since the individual does function as a total unit we may expect that there will be some evidences expressed not only psychologically but physically, of the presence of such conflicting wishes. Furthermore, it is a basic assumption that psychological wishes do not necessarily coincide with inherent biological drives. In other words, the fact that a woman

may have a biological capacity to bear a child does not mean that she wishes to do so or that she is psychologically capable of doing so in spite of her possible conscious professions that she does. One learns from psychiatric experience that many, many women consciously have no interest or desire ever to have a child; many others have unconscious aversion to pregnancy but express conscious desires based on illogical, immature, or even irrational considerations. In either case, one may expect that the mother or the child or both would suffer during pregnancy and that the conflict would display itself in a total organism reaction, both psychological and physiological."

2. Sex Adjustment.—In this series of patients no woman had a good sexual adjustment. Nine women had a fair adjustment (limited pleasure from sexual intercourse, but without orgasm or with only occasional orgasm.) The sex adjustment was considered to be poor in 43 patients. This group would be considered frigid by any standards and some complained of dyspareunia. Even taking into account the high incidence of frigidity or of relative frigidity in women in general, the incidence in this group of patients is definitely high. Frigidity is considered to be a significant predisposing factor.

3. Resentment Toward Husband.—Most women feel resentful toward their husbands at times; many women feel especially resentful toward their husbands during pregnancy. In this discussion I am not referring to this transient, situational resentment, but to more deeply rooted feelings of resentment pertaining to the husband-wife relationship. One of the most frequently expressed sources of resentment is passivity on the part of the husband. The wife complains about his lack of initiative and aggressivity, and feels that he fails to assume the emotional responsibilities of a husband (and father, if children are already present).

Forty-nine of the fifty-two patients (94 per cent) indicated such deep-seated, long-term resentment toward their husbands. This seems to be a significant predisposing factor. Smalldon[6] reviewed the records of 220 patients and found an incidence of 75 per cent hostility to the husbands. Undoubtedly this figure would have been higher if the patients had been more closely studied from this standpoint.

4. Menstrual Difficulties.—Thirty-one patients (60 per cent) gave histories of significant menstrual difficulties. Patients with only occasional or transient difficulties were not included in this group.

In an unpublished study of 2250 college girls, I found that 6 per cent of college girls *without* manifest emotional problems have menstrual difficulties, whereas 29 per cent *with* manifest emotional problems have menstrual difficulties. A comparison of the incidence of menstrual difficulties present in this group of 52 patients with the figures obtained in the college study strongly suggests a significantly high incidence of such disorders in the group that develops postpartum emotional illness.

In conjunction with the menstrual difficulties it is interesting that none of these 52 women felt they had received adequate preparation for menarche. Six had received fairly adequate preparation, 22 poor preparation, and 24 had received no preparation.

Psychopathology

These patients present many interesting and varied psychopathological features, some of which will be briefly discussed here.

The most frequently encountered emotional pattern in women relates to a basic unacceptance of the feminine role. Some women openly reject their feminine role in life, bitterly protesting the boredom of housework and motherhood. They bemoan their lack of opportunity for equality with men, resenting that they cannot do "interesting and stimulating work."

More often this rejection of the feminine role is subtle, and not directly verbalized. In this group the rejection reveals itself by such patterns as: frigidity, complete or partial; depreciatory attitudes toward feminine interests and activities; inability to do certain tasks usually thought of as feminine; avoidance of femininity in dress, make-up, hair style, and manner; being "one of the boys," rather than socializing with women. Marked flirtatiousness and promiscuity are often indicative of an underlying hostility to femininity.

A woman who consciously or unconsciously rejects her femininity is ill-prepared to assume the responsibilities of wifehood and of motherhood. Often such a woman will make a borderline adjustment to marriage, precariously maintaining her emotional equilibrium. When a child comes along, the added responsibilities tilt the scales of her emotional balance, and symptoms appear. Having a child often brings to the woman an acute awareness of her responsibilities as a wife and mother. She suddenly feels trapped in an emotional situation of which she has not previously allowed herself to be aware. She has always felt escape possible by separation or divorce or she could unconsciously pretend that she was still single. The arrival of the child changes this and the reality of her situation strikes. Her precarious adjustment gives way and symptoms appear.

Another frequently encountered emotional pattern in women who develop postpartum emotional illness is a "father complex." Such a woman has a strong underlying need for a father person (husband) to whom she can be a little girl who is taken care of and looked after. Strong dependency needs constantly seek direct gratification. A woman with this problem feels unable to care for a baby, feeling instead that she herself needs care. The baby may even represent competition for her husband's love and attention. She may then develop hostile, antagonistic feelings toward the baby. These hostile thoughts provoke fear and anxiety in the woman. Guilt feelings often appear and overt depression may be close behind.

A third frequently occurring psychopathological syndrome is that in which a woman has unresolved hatred toward her own mother. Associated with this conflict are underlying guilt feelings with associated self-depreciatory trends and depression. Related to the underlying hatred and fear of the mother, these patients usually reveal difficulties in any kind of competitive relationship with other women. Because of their residual problems relating to their own mothers, these women often find themselves unable to accept their own role as a mother. Becoming a mother is unconsciously the equivalent of aggressively replacing their own mother or of putting themselves into direct aggressive competition with her. Unless such a conflict can be satisfactorily resolved in psychotherapy, it is impossible for the woman fully to accept her role as a mother.

Many other psychopathological features enter into the understanding of individual patients with emotional illness. An individual patient usually presents a combination of basic conflicts, rather than just one clear-cut etiological syndrome.

Symptomatology

Emotional illness is characterized by its protean manifestations, presenting a wide variety of symptoms and symptom combinations. Quantitative and qualitative differences in symptoms are significant in the evaluation of a patient. In spite of these many variables, certain symptoms and symptom patterns do have diagnostic and prognostic significance.

Onset.—Some of the significant factors related to the onset of illness were discussed previously. In general, a slow, insidious onset is often associated with a less favorable prognosis. Conversely, an acute onset is often associated with a more favorable prognosis. There are many exceptions to these generali-

ties. In this context, the majority of patients in this study would be thought of as having an acute onset. A slow, insidious onset as used here indicates a disintegration of personality extending over many months or years.

In this study, 80 per cent of the patients had a subacute onset of illness, in contrast to the very abrupt, dramatic appearance of symptoms in the other 20 per cent. A less acute onset, as previously stated, is more typical of schizophrenia. This correlates with the fact that in this group of patients 75 per cent presented schizophrenic patterns of illness.

Depression.—The majority of patients who develop postpartum emotional illnesses show some amount of depression. If there is any one feature which tends to characterize this group of illnesses, it is this high incidence of affective involvement. This factor is important prognostically; it is generally true that the greater the affective involvement the better the prognosis. Depression is often the first sign of illness. Often the patient will complain of feeling blue, down in the dumps, discouraged, or that she doesn't care about anything. Lack of interest and enthusiasm is often a sign of depression.

Sleep difficulty may be a sign of impending depression or may be directly associated with overt depression. The most characteristic sleep difficulty in depressions is a consistent tendency to awaken early in the morning with inability to get back to sleep.

Feelings of inadequacy or of unworthiness may be expressed. The patient may verbalize guilt feelings which are not in keeping with reality. Any of these expressions of self-depreciation are ominous. If the guilt feelings are intensive enough, self-destructive drives appear and suicide is always a danger when depression is present.

Feelings of Unreality.—Women with postpartum emotional illnesses often complain of some kind of feelings of detachment. A patient may state that she is without any feelings. Feelings of unreality may be expressed in various ways: "I feel strange," or, "Everything about me appears to be strange or different," or, "I feel as though I am apart from myself, watching or observing myself," or, "I feel unreal and things about me seem unreal." The patient will indicate lack of feelings for the baby and for her husband. She will show no interest in caring for the baby, and will not be concerned about its welfare. This state represents a gross withdrawal of affect from the environment and is a distressing and serious symptom.

Feelings of estrangement or detachment are always of deep significance and are most often associated with schizophrenic patterns of reaction.

Abnormal Thought Content.—Disturbances in thought content are less common than other manifestations. The more acutely disturbed patients may reveal auditory hallucinations and delusional phenomena. When such gross thought disturbances are present there is no question about the fact that severe illness is present and that hospitalization is imperative.

Fears.—Anxiety in some form is very common. This often appears as a generalized feeling of apprehension or fear. At times the fear attaches itself to specific objects or situations; for example, fear of dying, fear that something is wrong with the baby, fear of people, fear of going outside, etc. Another way in which anxiety may manifest itself is in the form of panic attacks. These sudden attacks of uncontrollable panic occur without apparent cause and may appear at any time of the day or night. Such anxiety symptoms may be prodromal to a depression or schizophrenic reaction or may be symptomatic of a psychoneurosis.

Sleep Disturbances.—Very prominent in the array of possible symptomatology in these disorders is insomnia. The presence of a sleep disturbance in a postpartum patient should always be viewed as an indication of potential danger.

It is often the initial symptom in a developing illness. A postpartum patient who is having sleep difficulty should be carefully evaluated psychiatrically and should be closely observed. The sleep disturbance may take the form of difficulty in getting to sleep, which often is the forerunner of an anxiety type of reaction. It may manifest itself by repeated early awakening, which is often associated with a developing depressive reaction. The nature of the dream material is sometimes of diagnostic significance to the psychiatrist.

Suicide and Infanticide.—Suicide is always a potential danger in emotional illness, especially when depression is present.[7] The majority of this group of postpartum patients is depressed. Suicide is a particular concern in the evaluation of individual patients with postpartum illness. No figures are available as to the actual incidence of suicide in women with postpartum emotional illness, but it is not infrequent in these patients. Skottowe,[8] in a study of 26 cases, wrote that "two thirds of such cases showed a risk of infanticide or suicide at some stage."

Infanticide is tragedy at its worst. The incidence of this tragic expression of severe emotional illness is not known. Many times when a sick mother destroys her child the fact is covered up by the husband and by the doctor in order to avoid the impact of newspaper publicity and police investigation. Often an attempt is made to try to cover up or to hide the true nature of what has happened from the mother of the child, with the thought that she did it in a trance and does not realize what she did. Usually she realizes it only too well. Having destroyed her own child, she has a real reason to feel guilty and depressed and an almost impossible barrier to getting well has been established. Hopwood[9] and McIlroy[10] each found the incidence of infanticide to be highest during the lactation period.

Many new mothers are distressed by having hostile thoughts or feelings toward their newborn babies. When a woman expresses such thoughts, psychiatric evaluation should always be obtained. No generalization can be made about whether these hostile thoughts toward the baby might or might not be acted out. It is unfair to the woman to make light of them. It is naïve and ridiculous to try to reason her out of them. Such thoughts are always indicative of serious emotional illness.

Other Symptoms.—Many patients complain of severe chronic fatigue, along with which there is a generalized lack of interest and enthusiasm. Difficulty in concentrating and forgetfulness usually go together and occur rather frequently in these illnesses. A fear of "going crazy" or "losing my mind" is not infrequent and should be taken seriously. Empty reassurances that she is not losing her mind are of little avail in the face of such deep-seated and real fear. Many other symptoms are seen in individual patients and each symptom should be evaluated in the context of the total illness.

Course of Illness

The course of postpartum illnesses is, as could be expected, similar to the course of similar illnesses occurring under other circumstances. In general, it is true that an emotional illness which is precipitated rather acutely by a specific life situation has a better prognosis than an insidiously developing illness. This is true both in regard to the incidence of spontaneous recoveries and in regard to satisfactory response to treatment.

Figures are not available regarding the incidence of spontaneous recovery in postpartum emotional illness. It is undoubtedly true that many women who become ill remain at home without treatment and improve over a period of time. The time involved ranges from several weeks to several years. Many of these women remain sufficiently ill to be seriously handicapped in their daily living.

If treatment is not instituted rather promptly, many of the more extensively ill patients will become grossly disturbed and hospitalization will become imperative. Others will, if not treated, attempt suicide or harm their babies. It is dangerous to temporize with these illnesses.

Two rather frequent questions which arise in the general management of pregnant women who have developed a severe emotional illness are: (1) Should the pregnancy be interrupted? (2) Is it safe to give electric shock therapy during pregnancy?

The first question is controversial, but most psychiatrists are agreed that the pregnancy should not be interrupted because of emotional illness. In 1933 Robinson[11] polled 95 British psychiatrists, asking them if they felt that abortion should be done in pregnant women who become psychotic or in psychotic women who become pregnant. An overwhelming majority believed that abortion in these cases was not justified. Sometimes a woman who has had emotional illness following a previous pregnancy will appeal to the obstetrician to interrupt her current pregnancy. This should never be done.

A number of reports in the literature testify to the safety of giving electric shock therapy to pregnant women.[12] No instance has been reported in which the pregnancy has been harmed by the procedure. The risks for the woman appear to be the same as for nonpregnant women.

Treatment

After careful evaluation of the individual patient, a treatment program should be designed to suit her particular needs. There is no one treatment of choice. Certain general statements in regard to treatment have validity, however, provided one does not lose sight of the basic importance of selecting treatment in terms of individual needs. In general the following hold true: (1) In anxiety states and other psychoneurotic patterns of reaction, psychotherapy is the treatment of choice. (2) In depressed patients who are inaccessible to psychotherapy, electric shock treatment will have most to offer. The inaccessibility may be because of the depth of the depression or because of conscious rejection of psychotherapy by the patient. (3) In schizophrenic reactions, psychotherapy may be indicated in the less severe reactions. Some of these women do not need hospitalization and are able to accept the responsibilities of psychotherapy. Such patients often utilize the treatment effectively in working out their problems, thereby ridding themselves of symptoms. The schizophrenic group which requires hospital care does best with insulin coma therapy, sometimes combined with electric shock.

Whenever possible, patients who have been treated by insulin coma therapy or by electric shock treatment should follow up such treatment with psychotherapy. The somatic therapies produce symptomatic improvement but do not solve the underlying problems. Unless those problems are worked out in follow-up psychotherapy, recurrence of symptoms is all too frequent.

In this series of patients, 84.7 per cent improved with treatment. Nineteen patients (36.5 per cent) were greatly improved, and twenty-five patients (48.2 per cent) showed varying degrees of improvement. Three patients (5.7 per cent) were unimproved and five patients (9.6 per cent) left the hospital against advice. Boyd states that the prognosis for recovery of the whole group of major puerperal psychoses is about 70 to 75 per cent. He adds that when dealing with schizophrenic patients the figure will be much lower.

Table I presents a breakdown of the treatment used for the patients in this study and the results obtained in each group.

All studies of treatment results agree upon one fact: the earlier treatment is instituted, the better the prognosis. This applies to all types of treatment. A

typical example of this very important principle comes from Kalinowsky's[13] study of 275 patients: The remission rate in patients with illness of less than six months' duration was 68.3 per cent; 41.5 per cent in those ill from six months to two years; and only 9.2 per cent in those ill more than two years. Patients with a longer history but with previous remissions have a rather favorable prognosis for the new attack (56.6 per cent remissions).

TABLE I. TREATMENT

TREATMENT	NO. OF PATIENTS	GREATLY IMPROVED	IMPROVED	UNIMPROVED
Electric shock	18	8	8	2
Insulin coma	3	1	2	
Insulin and electric shock treatment	8	3	4	1
Psychotherapy	10	4	6	

Additional Pregnancies

Should a woman who has suffered a definite emotional illness following a pregnancy experience have more children? Various opinions are expressed about this in the literature. The trend of the opinions seems to be that the woman should wait about two years after she has recovered from her illness. If in that time there has been no recurrence of illness and she very much wants another pregnancy, she may go ahead with it. It is recognized that such a woman takes a definite risk of becoming ill again. Some psychiatrists feel that additional pregnancies are absolutely contraindicated, especially in schizophrenia. If the woman works out her problems in intensive psychotherapy, she should be able to have additional pregnancies with impunity.

Actually, the question of whether a woman should have additional pregnancies or not should be decided on the merits of the individual case. In general, though, the two-year waiting period is sound advice and should be given in most instances. The patient and her husband should both be directly advised of the dangers of additional pregnancies because basically the responsibility for such a decision rests with them.

Implications of the Problem

It is evident that postpartum emotional illness is a very significant medical problem. This is true not only from the psychiatric viewpoint, but from the general medical and obstetrical viewpoints as well. The problem has widespread social implications because of the impact of an emotionally ill mother upon her children. Symptoms of emotional illness following childbirth should be taken just as seriously as should uterine bleeding or infection.

The general medical man and the obstetrician have a definite responsibility in relationship to this problem of postpartum emotional illness: (1) to become acquainted with the nature of the problem, (2) to detect early signs and symptoms of illness, (3) to alleviate certain kinds of emotional stress during pregnancy, (4) to prevent suicide and infanticide, (5) to predict the possibility of psychosis and its possible implications for future childbearing, (6) to avoid advice to emotionally upset women to get pregnant as a solution for their difficulties, (7) to insist on psychiatric consultation when it is indicated. In regard to this last, it often happens that the patient or her family will resist accepting consultation. If the doctor permits them to persuade him not to insist on such consultation, he places himself in the position of being criticized by the relatives if suicide or infanticide occurs. In an attempt to avoid their own guilt feelings, they will say to the doctor, "You should have insisted on it. We didn't realize how serious it was."

Summary

1. Although studies of institutionalized patients indicate an incidence of one psychosis in 400 confinements, the over-all evidence suggests that about 5 per cent of women who become pregnant will have some form of emotional illness following the birth of one of their children. Nine per cent of women who become psychotic do so in conjunction with a reproductive experience.

2. Pregnancy and childbirth act as precipitating rather than causative factors in the production of these illnesses. The same diagnostic categories of emotional illnesses are seen post partum as are seen in other situations. The typical distribution of diagnostic categories is controversial, but there appears to be a high incidence of schizophrenic reactions with a large affective component.

3. About 25 per cent of these patients manifest their illness during pregnancy, the other 75 per cent becoming overtly ill post partum. The onset is gradual in about 80 per cent and symptoms may not become apparent for even 6 to 10 months post partum.

4. Important predisposing factors are: (1) negative attitudes toward pregnancy, (2) frigidity, (3) deep-seated hostility toward the husband, (4) a history of menstrual maladjustment.

5. Conflicts over acceptance of the feminine role, over the father relationship, and over the mother relationship are commonly encountered in these patients and play important roles in the production of the illness.

6. Symptomatology is protean in its manifestations. Some of the more important symptoms are discussed here.

7. The course of the illness depends upon the type of illness, the nature of the psychopathology, the individual in whom the illness occurs, and the type of treatment program.

8. Treatment must be highly individualized. In general, psychotherapy is the treatment of choice. Insulin therapy is often helpful in the schizophrenic reactions, while electric shock is often indicated in the severe depressions.

9. A knowledge and understanding of this problem are essential to the general physician and to the obstetrician. Early detection of these conditions, and of the potential for developing these conditions, will serve the causes of prevention, early treatment, and avoidance of suicide and infanticide.

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COAGULATION DEFECTS IN OBSTETRIC SHOCK: MECONIUM EMBOLISM AND HEPARIN; FIBRIN EMBOLISM AND DEFIBRINATION*

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THE present purpose is to investigate the possible presence of one or more circulating anticoagulants during the hemorrhagic diatheses of two kinds of obstetric shock: the shock of amniotic embolism, and the shock of abruptio placentae. The study was done in large part with the aid of laboratory experiments.

The laboratory equivalent of one kind of maternal amniotic embolism is the meconium embolism which can be induced in animals.[52] It was found previously that during the shock of meconium embolism in dogs, a heparin-like anticoagulant is released into the circulation.[43] Later, this anticoagulant will be demonstrated truly to be heparin.

By comparison, a "thrombin-inhibitory" activity has been demonstrated in a proved case of human amniotic embolism.[28] The question arises whether this anticoagulant effect may be due to heparin which acts as an inhibitor of coagulation, or to a true antithrombin in the sense of an inactivator of thrombin.

Obstetric shock comparable to that of amniotic embolism probably also occurs in abruptio placentae. This appears to be the result of a peculiar kind of disseminated intravascular coagulation.[39] Induced, widespread intravascular coagulation has been reported to result in an increase of an unspecified kind of antithrombin activity in animals.[10, 27] The problem arises whether there may be an increase of an antithrombin activity, heparin-like or otherwise, during abruptio placentae.

The present experimental investigations and pathogenetic interpretations are of interest to problems of hemostasis and of hemorrhage, as well as to the resolution of possible pulmonary hypertension and shock, during maternal amniotic embolism and during abruptio placentae.

Orientation

Specific Assay for Heparin.—To demonstrate the presence of heparin in experimental meconium embolism it was necessary to use an assay method known to be specific[21] for heparin.† This is because the previously used[43] protamine titration and the toluidine-blue titration, although together highly suggestive of the presence of heparin, are not necessarily specific for it.

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†Heparin assays were performed through the courtesy of Dr. Frank C. Monkhouse, of the Department of Physiology, University of Toronto, Canada (now at Wayne University College of Medicine, Detroit, Mich.).

The specific assay for heparin is even more essential for study of fibrin embolism, during which the coagulation itself results in a "biphasic" variation such that the coagulation time first decreases and then increases, a variation which renders interpretation of the protamine titration unsatisfactory.

Mechanisms of Obstetric Shock.—In abruptio placentae, *fibrin embolism* (disseminated formation and embolism of minute fibrin filaments within the circulating blood itself) may result in the deposition of fibrin intravascularly, leading to widespread building up in situ of intravascular occlusions of fibrin.[39] These fibrin occlusions may tend to build up especially in the pulmonary vascular bed.

By contrast, in the clinical entity, amniotic embolism, there is disseminated pulmonary embolism of *preformed* debris. The offending debris, carried in suspension in amniotic fluid, may be largely squamae and vernix caseosa; in fatal cases the bulk of the debris is frequently meconium which has become accidentally discharged from the fetus into the amniotic fluid.[52] When meconium suspensions are injected intravenously into experimental animals, the morbid physiologic process, *meconium embolism* leads directly to disseminated occlusion of the pulmonary vascular bed.

The shock of amniotic embolism and that of abruptio placentae are probably of sufficiently specific and similar characteristics to be referred to together under the generic term "obstetric shock." Likewise, despite the diversity of origin of meconium embolism and of fibrin embolism, and despite the diversity of the manner in which these may lead to formation of vascular occlusions, the vascular occlusions have much in common as to acute course, and as to size and distribution of the occlusions throughout the pulmonary vascular bed.[39, 52] The resultant disorders may include sudden failure of the circulation and acute cor pulmonale.[38, 47, 52]

Curiously, in addition, each of the processes may result in failure of coagulation of the circulating blood, but this also by opposite mechanisms.[43]

Mechanisms of Hemorrhagic Diathesis.—In the present investigations, plasma from patients with different degrees of severity of clinical reaction and of defibrination during abruptio placentae were available for analysis, but no specimen of plasma from a patient with maternal amniotic embolism was available for complete rounding out of the investigation. This leaves an unanswered question in our understanding of the long-suspected[52] but only recently proved failure of coagulation in amniotic embolism.[7, 8, 28] Ratnoff and Vosburgh[28] believe this failure of coagulation to be due, in part, to an inhibition of coagulation by a kind of thrombin-inhibitory activity. It would be premature to conclude whether the antithrombin activity which Ratnoff and Vosburgh demonstrated may be due to release of heparin into the circulation or whether the apparent inhibition in the human being may be of some different origin.

Coagulation of Fibrin.—So far as the underlying biochemical processes of coagulation are concerned, one effective mechanism for the coagulation of fibrinogen to fibrin may be represented as shown in Fig. 1, *A*. This is the mechanism of coagulation in the present experiments. In the first stage of coagulation, in a system of isolated reagents, several activators (not all of them shown in Fig. 1, *A*) tend to promote the conversion of prothrombin to thrombin. (The thromboplastin which initiates this conversion, Fig. 1, *A*, is understood to be tissue thromboplastin.) In a second stage, thrombin converts fibrinogen to fibrin (Fig. 1, *A*). In a final stage, the fibrin forms a fibrin clot.

In a test-tube mixture of blood and tissue extract and also in a circulating mixture as in the present experiments, the first stage of the fibrin coagulation of Fig. 1, *A*, may be initiated by the tissue thromboplastin from the tissue ex-

tract. Of course, coagulation, particularly the physiologic coagulation of hemostasis, may be initiated by other mechanisms, including a platelet mechanism, but fibrin embolism apparently tends to be unique in its initiation by tissue thromboplastin.[46] For comparison it may be mentioned that fibrin embolism is not initiated by injection of platelet extracts.[45]

Certain inhibitors may tend to retard or to prevent the coagulation mechanism (Fig. 1, *A*). Among these, heparin inhibits both the activation of thrombin by thromboplastin and the conversion of fibrinogen to fibrin by thrombin. Heparin is not normally present in blood; Dr. Monkhouse[22] reminds us that heparin has yet to be demonstrated by specific assays in human blood either in normal or in pathologic conditions.

A true antithrombin activity is normally present in the plasma in high activity. Antithrombin acts by destroying thrombin itself[49] (Fig. 1, *A*).

Lysis of Fibrin.—Destruction of a fibrin clot by fibrinolysis may be considered to occur by a mechanism (Fig. 1, *B*) somewhat parallel to that for coagulation. The profibrinolysin in the blood may be activated, and secondarily the fibrinolysin so released may cause destruction of fibrin or indeed of fibrinogen. Activation of fibrinolysin of the blood may be initiated in different ways, including activation by tissue fibrinokinase from tissue extracts (Fig. 1, *B*), and in some obscure way during certain kinds of fatal shock.

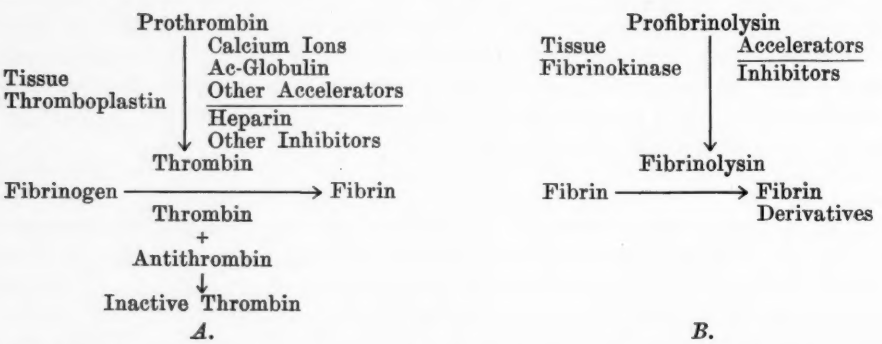

Fig. 1.—Mechanisms of fibrin coagulation and of fibrinolysis (modified after Seegers).

A, Coagulation. This is a mechanism of blood coagulation which can be studied in an isolated system in the laboratory. It is also probably the mechanism of coagulation which occurs throughout the circulating blood when tissue thromboplastin is introduced experimentally into the circulation in animals, or when it is introduced spontaneously into the maternal circulation during abruptio placentae. A characteristic kind of disseminated fibrin deposition may follow this intravascular coagulation.

B, Fibrinolysis. Profibrinolysin, the precursor of fibrinolysin, and perhaps accelerators for its conversion to fibrinolysin, are present in the plasma. Fibrinokinase, the initiator of the conversion, may be derived from an external source such as certain tissue extracts. Fibrinolysin may attack not only fibrin but fibrinogen as well. It is not excluded that massive disseminated intravascular coagulation may somehow result secondarily in activation of fibrinolysin; the fibrin deposits are soon lysed away.

Coagulation of the Circulating Blood.—In so far as the individual is concerned, other processes in conjunction with the biochemical mechanisms of coagulation and of lysis of the coagulum (Fig. 1) are important. In this respect the multiple role of the platelets, including the agglutination of platelets and the release of a potent vasoconstrictor, must not be forgotten.

The fibrin coagulation of Fig. 1, *A*, is a *plasma* coagulation mechanism. Although usually contributing to thrombus formation in mammals, fibrin coagulation has no necessary relation to "pure" thrombus formation. For example, in primitive organisms which lack a plasma-coagulation mechanism, hemostasis may be accomplished by a kind of thrombus formation by agglu-

tination of amebocytes which may be regarded in certain respects as a primitive type of platelet or thrombocyte.[1] Similarly, in the human being with congenital afibrinogenemia, functional thrombi may be formed from platelets alone.[2] A coagulable component within platelets themselves[46] may be of significance. Conversely, and pertinent to considerations as a pathogenetic process in abruptio placentae, the coagulation mechanism of Fig. 1, *A*, may lead to "fibrin embolism" and thereby to fibrin plug formation. These fibrin plugs may be quite the converse of thrombus formation in that the component of platelets may be a minor one, i.e., the vascular occlusions may be made up essentially from plasma fibrin deposits.

The remaining, circulating "blood," as a result of the removal of fibrinogen by coagulation, may thereby become a suspension of formed elements, not within plasma, but essentially within serum[44] (Table I).

TABLE I. COMPARISON OF CIRCULATING "PLASMA"* OF CLINICALLY SEVERE ABRUPTIO PLACENTAE WITH SERUM FROM AN ORDINARY TEST-TUBE BLOOD CLOT. VALUES IN PER CENT OF NORMAL

CONTENT IN PER CENT OF NORMAL PLASMA	PARENT PLASMA IN TEST TUBE	SERUM IN TEST TUBE	CIRCULATING "PLASMA" OF SEVERE ABRUPTIO PLACENTAE
Fibrinogen	100	0	≅ 20[5, ,24, 39]
Prothrombin	100	20[59]	≅ 50[14, 39]
Ac-globulin	100	7[60]	≅ 10[14]
Antithrombin	100	Mild decrease (delayed)	Mild decrease (delayed)

*The circulating "plasma" is essentially serum.

Because of the capacity of tissue thromboplastin to initiate coagulation rapidly enough to cause acutely lethal coagulation, and, secondarily, acute failure of hemostasis, thromboplastin may still be referred to as a "toxin." The intravascular coagulation of the present experiments (and presumably also that of abruptio placentae) is a pathologic coagulation not merely because of its initiation by tissue thromboplastin but because this can lead to massive and widespread formation of fibrin within, and deposited from within, the circulating blood.

Methods

Inhibition of coagulation by heparin and by true antithrombin was searched for in obstetrical shock of maternal abruptio placentae, and in dogs in which comparable shock was induced experimentally by intravenous injection of tissue thromboplastin from crude bovine lung tissue extract. The changes were compared and contrasted with those occurring after intravenous injection of meconium suspension into dogs. The dogs were anesthetized with Nembutal.

Human meconium suspension was made up as a 1:10 dilution in saline and was injected rapidly in a single dose as before[43, 47] to cause meconium embolism.[52]

In previous investigations, when thromboplastin was injected,[34, 35] this also was usually as a single dose. When a large, but just sublethal, dose is thus given rapidly, acute shock results.[34-47] Even after the most severe reaction, there may be early recovery from the shock—recovery within five minutes[34, 35, 47]; even as much as five minutes of shock, however, is a short interval when compared with the duration of shock of meconium embolism[52] (compare Figs. 1 and 2 of Schneider and Engstrom[47]). Hence, in order to obtain shock of duration more comparable to that which occurs in meconium embolism, in a few ad-

ditional dogs thromboplastin was injected slowly as an infusion (rather than as a single massive dose) as in the experiments of Page, Fulton, and Glendening[24]; this required a several-fold larger total dose of thromboplastin. The rate of infusion was adequate to result in reduction of the aortic pressure to 50 mm. of mercury and to maintain the pressure at or near this level for many minutes. Alternatively, in some animals, repeated doses were given.

As a control study, peptone shock was produced by intravenous injection of Bacto Protone (Difco), as a 5 per cent solution in saline. A single dose of 250 mg. per kilogram of body weight was infused rapidly into an anesthetized dog; this caused severe peptone shock for one-half hour or longer. Before injection, the solution was clarified of a small amount of flocculant residue by centrifugation.

Samples of plasma were obtained during the course of the different kinds of experimental shock. Samples of stored plasma from women in obstetric shock of spontaneously occurring abruptio placentae were also obtained. All samples were collected by a two-syring technique: A small amount of venous blood was drawn into the first syringe to clear the needle of tissue juices. Then the first syringe was replaced by the second which contained 1 ml. of 3.2 per cent sodium citrate; 9 ml. of whole blood was drawn through the needle into the anticoagulant. The plasma from this blood was separated and was frozen at minus 20° C. until assayed. On the accumulated samples, heparin and antithrombin were assayed according to standard specific procedures, respectively.[21, 49]

It can be deduced from the data of Tables II to IX, that both the heparin activity and the antithrombin activity were well preserved during storage in the frozen state. This is in contrast to the spontaneous loss of antithrombin activity when plasma is stored in the cold, but not frozen.[49] It follows that the frozen specimens were satisfactory for the present studies.

Results

Part I. Heparin Release.—

Preliminary investigation: As a control study, shock was induced by the injection of peptone. After 15 minutes of peptone shock, the blood contained a high level of heparin, 0.30 unit per milliliter of plasma. Control specimens of plasma contained no heparin. This tended to establish the validity of the experimental techniques.

Experimental meconium embolism: Heparin appeared in the blood during the shock of meconium embolism (Table II).

TABLE II. HEPARIN CONTENT OF BLOOD OF DOGS DURING SHOCK AFTER INJECTION OF MECONIUM SUSPENSION

DOG	DOSE OF MECONIUM	TIME, MINUTES AFTER INJECTION	HEPARIN, UNITS PER ML. OF PLASMA
1	Sublethal	Control	< 0.01
		10	0.33
		20	0.24
2	Sublethal	15	0.07
		40	0.30
3	Lethal	7	1.0

The concentration of heparin was a function of the degree of the shock and thereby also of the dose of meconium (Table II). With small doses the coagulation time was not prolonged.[43] With sublethal doses adequate to cause severe shock, the coagulation time was prolonged and the concentration of heparin in the plasma was as great as that during shock caused by injection of peptone. After shock from the lethal dose of meconium, the concentration of heparin was three times as great as in sublethal experiments (Table II).

Experimental fibrin embolism: There was no detectable release of heparin into the circulation during shock caused by injection of tissue thromboplastin (Table III).

TABLE III. FAILURE TO DETECT HEPARIN IN THE BLOOD OF DOGS DURING SHOCK AFTER FIBRIN EMBOLISM FROM INTRAVASCULAR COAGULATION CAUSED BY INJECTION OF THROMBOPLASTIN

DOG	DOSE OF THROMBOPLASTIN	TIME, MINUTES AFTER INJECTION	HEPARIN, UNITS PER ML. OF PLASMA
4	Sublethal	Control	< 0.01
		10	< 0.01
		22	< 0.01
		48	< 0.01
5	Lethal	10	< 0.01

Maternal abruptio placentae: Clinical and pathologic evidence leads to the conclusion that fibrin embolism occurs in maternal abruptio placentae.[37-47] (Conceivably this may be the cause of severe, or of fatal, obstetrical shock.[39]) It is also probable that fibrin embolism occurs in at least some cases of eclampsia.[39] There was no detectable release of heparin in association with eclampsia or with abruptio (Table IV).

TABLE IV. FAILURE TO DETECT HEPARIN IN THE BLOOD STREAM OF WOMEN WITH ECLAMPSIA OR WITH ABRUPTIO PLACENTAE

CASE	CLINICAL CONDITION	TIME, HOURS AFTER ONSET	HEPARIN, UNITS PER ML. OF PLASMA
1. HKH—109110	Eclampsia	0	< 0.01
2. WH—091453	Eclampsia	2	< 0.01
3. HKH—106440	Abruptio placentae, severe	4	< 0.01
4. HKH—107299	Abruptio placentae, moderate	6	< 0.01
HKH—107299	Abruptio placentae, moderate	7	< 0.01

Summary of findings of release of heparin: Doses of meconium suspension sufficiently large to cause shock were injected intravenously into dogs. Prompt release of heparin into the circulating blood followed.

During similar shock caused in dogs by fibrin embolism, initiated by intravenous injection of thromboplastin, there was no release of heparin.

Consistent with these observations on the experimental animals, during the shock of human abruptio placentae no release of heparin was found.

TABLE V. SUMMARY OF RELEASE OF HEPARIN IN SHOCK OF MECONIUM EMBOLISM AND OF FIBRIN EMBOLISM

DISORDER	EXPERIMENTAL	OBSTETRIC
Fibrin embolism	No heparin	No heparin
Meconium embolism	Heparin present	(Not measured)*

*Dr. Monkhouse[22] reminds us that "release of heparin is not likely to occur as readily in the human as in the dog since methods of extraction which yield large quantities of heparin from dog tissue fail when applied to human tissue."

No plasma obtained during amniotic fluid embolism was available for study.

Compilation of the observations (Table V) leads to the question whether, following clinically severe maternal *meconium* embolism, if indeed not following any severe *amniotic* embolism, there may be release of heparin into the circulation.*

*See footnote under Table V.

Part II. Antithrombin.—

Preliminary investigation: The measurement of an over-all antithrombin activity has long been a troublesome and uncertain procedure, not reduced to quantitative terms. A method for measuring "true" antithrombin in the sense of an inactivator of thrombin has been devised[49]; this is subject to the technical difficulties inherent in any second-order procedure. Even this assay has not been calibrated in terms of "units" of antithrombin, and it seems to be sensitive to the activities of accelerators.[48]

Several kinds of "antithrombin" activities are considered to occur.[26, 48, 49] For the present purpose the first of these antithrombin activities, that by adsorption of thrombin upon fibrin,[26] may be ignored for there is no evidence that coagulation of fibrin occurs in meconium or in amniotic embolism.[43, 44] The second antithrombin activity, that of heparin (together with its plasma cofactor), exerts an inhibiting effect upon thrombin, but not an inactivation of thrombin. This heparin activity has already been assayed specifically and separately in the first section of this investigation. There remains still to be measured that antithrombin which *inactivates* thrombin[49] and which in this sense might be referred to as a true antithrombin.

An essential reagent for the demonstration of this antithrombin is purified thrombin, activated from purified prothrombin with citrate. Measurement of this antithrombin activity is not interfered with by the addition of purified heparin.[49] In the assay, a concentration of thrombin substrate was employed, which was approximately optimal for evaluation in the range of antithrombin activity under investigation.* In an orientation experiment, there was 56 per cent inactivation of the thrombin substrate by plasma obtained from a dog during peptone shock. This blood, as confirmed in the first section of this paper, contained heparin. Since the percentage inactivation of thrombin was essentially the same as that brought about by control dog plasma (Table VI) it seems probable that this antithrombin assay was valid in the presence of naturally occurring heparin, and that its use should be valid in the investigations below, whether or not heparin was also present.

TABLE VI. ANTITHROMBIN ACTIVITY: PERCENTAGE INACTIVATION OF THROMBIN* BY PLASMA COLLECTED DURING SHOCK OF MECONIUM EMBOLISM IN DOGS

DOG	DOSE OF THROMBOPLASTIN	TIME, MINUTES AFTER INJECTION	HEMOLYSIS IN PLASMA	PERCENTAGE OF THROMBIN INACTIVATED
6	Sublethal	Control	–	60
		15	–	55
		40	–	56
7	Sublethal	Control	–	54
		20	–	58

*The final reaction mixture of diluted, defibrinated plasma and purified thrombin, contained approximately 420 units of thrombin per milliliter.

Antithrombin during shock of meconium embolism in dogs: The order of magnitude of the antithrombin activity of plasma collected during shock of meconium embolism in dogs can be interpreted from the data of Table VI; as can be seen, here also the concentration of thrombin substrate that was chosen was optimal for the assay. The differences of the thrombin activity before and shortly after the meconium embolism were within the limits of experimental error of the method. Hence, there was no evidence of significant change of true antithrombin activity during the shock of experimental meconium embolism.

*Certain of the assays were performed by Nevenka Ivanovich; she also gave instruction in the technique of the assay.

Antithrombin during shock of fibrin embolism in dogs: The order of magnitude of the antithrombin activity of plasma collected after injection of tissue thromboplastin into dogs can be interpreted from the data of Table VII.

TABLE VII. ANTITHROMBIN ACTIVITY: PERCENTAGE INACTIVATION OF THROMBIN BY PLASMA COLLECTED FOLLOWING SHOCK OF FIBRIN EMBOLISM IN DOGS CAUSED BY INTRAVENOUS INJECTION OF TISSUE THROMBOPLASTIN

DOG	DOSE OF THROMBOPLASTIN	TIME AFTER INJECTION	HEMOLYSIS IN PLASMA	PERCENTAGE OF THROMBIN INACTIVATED
8	Sublethal	Control	–	62
	(single	½ hour	+	72
	injection)	1 hour	+	74
		1 day	–	78
9	Sublethal	Control	–	82
	(multiple	1 hour	+	74
	injection)	1 day	–	84
10	Sublethal	Control	–	74
	(multiple	½ hour	+	76
	injection)	1½ hours	+	54
		4 hours	+	48
		2 days	–	78
		3 days	–	88

No marked trend of change of antithrombin activity, in association with the interval of shock following fibrin embolism, is evident. In the one dog, No. 10, with intermediately spaced determinations, there seemed to have been an appreciable decrease of the over-all antithrombin activity as measured by this assay, some hours after the injections of thromboplastin extract. After a day or more there appeared to have been a slight but real increase of antithrombin activity. From the data presented, no precise accounting is possible as to whether the observed decrease and subseqent increase of antithrombin activity, after injection of thromboplastin, was due to actual changes of antithrombin itself or perhaps to changes of antithrombin accelerators or inhibitors.

Antithrombin and maternal abruptio placentae: The antithrombin activity of plasma collected at different intervals after the spontaneous onset of abruptio placentae is given in Table VIII.

CASE 5.—There was no hemolysis; the plasma fibrinogen did not fall below 250 mg. per cent. The abruptio placentae ran a moderately severe course as evaluated by clinical signs, and was terminated by cesarean section before the condition became severe. In this case of abruptio there was little or no evidence of change of antithrombin activity; the activity was comparable to that of blood of normal maternity patients without abruptio (see Table VIII).

CASE 6.—The clinical course of the abruptio placentae was severe; in addition there was marked intravascular hemolysis; the fibrinogen level fell as low as 60 mg. per cent. There appeared to be a real decrease of antithrombin activity at least within a few hours following the abruptio placentae, and then a subsequent rise a few days post partum (Table VIII).

Summary of antithrombin after fibrin embolism and after meconium embolism: Some time after severe, disseminated intravascular coagulation, whether initiated in dogs by the injection of thromboplastin or in women by abruptio placentae during late pregnancy, presumably as a result of spontaneous autoextraction of decidual thromboplastin into the maternal circulation,[35-47] there appeared to be a mild decrease of antithrombin in the circulating blood. During the next few days, the antithrombin activity increased somewhat above normal. The changes appeared slowly, neither the increase nor the decrease developing during the shock; both were of small magnitude.

By contrast to these small changes of antithrombin activity following fibrin embolism, there was no significant change at all following experimental meconium embolism in dogs, and this despite the marked release of heparin into the circulation during the shock of meconium embolism. In the experimental animals, the presence of the heparin did not interfere with the assay for true antithrombin activity; i.e., did not interfere with the assay of that antithrombin activity which inactivates thrombin.

No blood specimens from women with meconium embolism or with other amniotic embolism were available for the present studies.

TABLE VIII. ANTITHROMBIN ACTIVITY: PERCENTAGE INACTIVATION OF THROMBIN BY PLASMA COLLECTED AFTER ONSET OF MATERNAL ABRUPTIO PLACENTAE

CASE	TIME, HOURS AFTER ONSET OF ABRUPTIO	HEMOLYSIS	PERCENTAGE OF THROMBIN INACTIVATED
5. HKH—119623	Jan. 30, 1952		
Abruptio placentae	4	–	72
	5	–	82
	6	–	84
	12	–	84
	36	–	82
Control patient in labor	Jan. 30, 1952 Control	–	86
	Control (2 hr. later)	–	86
6. HKH—97778	Dec. 30, 1951		
Abruptio placentae	6	–	30
	8	–	38
	10	+	36
	14	+	40
	22	–	42
	2 days	–	64
	5 days	–	72
	9 days	–	52
Control patient undelivered	Dec. 31, 1951	–	60
Control patient midlabor	Jan. 26, 1952	–	50

One case of abruptio placentae was severe enough to have marked hemolysis and defibrination, the other was without hemolysis and with only partial defibrination. Determinations from normal patients are included for comparison.

Compilation of the observations (Table IX) leads to the suggestion that, when specific assay methods for true antithrombin activity are applied to plasma from women with meconium embolism or from other proved cases of maternal amniotic embolism, no change of true antithrombin activity will be found.

TABLE IX. SUMMARY OF ANTITHROMBIN ACTIVITY FOLLOWING INTRAVASCULAR COAGULATION FROM EXPERIMENTAL INJECTION OF THROMBOPLASTIN INTO DOGS AND FOLLOWING MATERNAL ABRUPTIO PLACENTAE

	EXPERIMENTAL	MATERNAL
Fibrin embolism	Tendency: temporary decrease, subsequent increase	Tendency: temporary decrease, subsequent increase
Meconium embolism	Unchanged	(Not measured)*

*From the data of this table it is to be predicted that there will be no influence upon the antithrombin activity by the shock of maternal meconium embolism or of other amniotic embolism.

Comment

Anaphylactoid Shock.—In the original description of maternal amniotic embolism and of experimental meconium embolism, Steiner and Lushbaugh[52] applied the term "anaphylactoid shock." This term was used to characterize the peculiar clinical disorders associated with the pathologic changes they had discovered. By use of this terminology, they carefully distinguished the etiological process from anaphylactic shock. Similarly precise use of the term anaphylactoid shock has not always been observed by writers who subsequently quoted them.

The term "anaphylactoid shock" characterized the over-all clinical reaction of the individual. The term does not necessarily imply a toxic component, as contrasted with a morbid, disseminated, embolic component, although either or both processes may have been concerned in the pathogenesis of the shock.

By contrast, among students of immunology, the term "anaphylactoid shock" has also been defined on another rather precise basis from analogy to anaphylactic shock, the definition being in terms of the characteristic effector organ involved, a peculiarity being that the effector organ is different, in various laboratory animal species. In the guinea pig, the reaction is said to be predominantly one of bronchospasm; in the rabbit, pulmonary arteriolar spasm; in the dog, vasospasm of sphincters in the liver.

Susceptibility to the mediating substance is immunologically induced in anaphylactic shock. By contrast, susceptibility is in some way inherently present, without the necessity of prior sensitization to the exciting agent in the kind of anaphylactoid shock that is of interest to the immunologist. The reaction may follow acutely upon introduction of a substance to which there has been no known previous sensitization. Such a simple substance as benzene may cause the shock.[51]

This special definition of the immunologist of the term anaphylactoid shock[51] is not in conflict with the sense in which Steiner and Lushbaugh considered amniotic fluid embolism; it is not necessarily applicable to their problem; neither was it excluded by them. Instead, they were concerned primarily with disseminated pulmonary vascular occlusion. They considered this occlusion in amniotic embolism to be of complex origin, based on disseminated embolism, but recognized a probable contributing element of vasospasm as well. They did not invoke the presence of a toxin to account for the vasospasm because separate experiments did not demonstrate a toxic component; they did consider the possibility of some physiologic mediation of vasospasm. They recognized as an end result that there could be acute dilatation of the right side of the heart (acute cor pulmonale).

The nonspecific sense of the term "anaphylactoid shock," as used by Steiner and Lushbaugh, is a confirmation and an extension of the sense in which Hanzlik and Karsner[12] understood the phenomena of anaphylactoid shock, which they studied in experimental animals after intravenous introduction of a variety of materials. Hanzlik and Karsner injected, besides dissolved crystalloids and colloids, various kinds of suspended debris including finely divided clay. It is to be noted that among other materials they also injected lung tissue extracts and other tissue extracts which doubtless caused acutely and widely disseminated coagulation, as in the fibrin embolism experiments reported previously.[39] Their interest was directed toward the similarity of the end result upon the individual and not toward the possible diversity of pathogenetic mechanisms.

It is perhaps not surprising that amniotic embolism and its description as an anaphylactoid response is sufficiently complex to have led to misunderstandings and to some misquotations. Despite direct quotations to the contrary, Steiner and Lushbaubh did not ascribe death to an "anaphylactic"[29, 30]

reaction, nor to "toxicity"[30] of the amniotic fluid—interpretations of a kind which led a recent group of investigators, Cron, Kilkenny, Wirthwein, and Evrard,[3] to perform critical experiments in which meconium was injected into a major branch of the arterial circulation rather than into the venous circulation. As was to be expected in their experiments, local embolization from a femoral artery caused regional failure of the circulation distal to the injection; there was no severe systemic reaction. Cron, Kilkenny, Wirthwein, and Evrard concluded that "pulmonary embolism rather than anaphylactic shock is productive of death in amniotic fluid pulmonary embolism." This conclusion was arrived at by exclusion of any overwhelming toxic effect by itself alone. That pulmonary embolism is the pathogenetic process confirms and is the underlying interpretation of Steiner and Lushbaugh also.

A primary aspect of a pulmonary vascular occlusive mechanism as a cause of anaphylactoid shock has been studied in some detail by Gross and Brown.[11] They studied the pathogenesis of a state of anaphylactoid shock in rabbits following the injection intravascularly of minutely divided clay particles. The particles were far too small to cause circulatory obstruction, of and by themselves. Nevertheless, disseminated occlusions of the pulmonary vascular bed by proteinaceous masses were visible microscopically. Gross and Brown interpreted these masses as having been built up by aggregation of plasma-protein-coated particles of clay. Hence, these investigators supported the interpretation that a pathogenetic process of anaphylactoid shock may include importantly an element of anatomic intravascular occlusions of the pulmonary circulation. In unreported experiments similar to those of Gross and Brown, we have confirmed the presence of proteinaceous masses in pulmonary capillaries and arterioles. These developed after injection of particles of kaolin or of other materials of submicroscopic size, far too small in themselves to cause the observed occlusions, and occurred not only in regions of phagocytic vascular endothelium in the lung, but also in the liver, spleen, and bone marrow.

The present investigations on the release of heparin do not serve to clarify the question of the precise pathogenesis of the shock during amniotic embolism. No interpretation with a bearing on this question is possible, because, first, in dogs a frequently observed response to anaphylactoid shock of diverse origins (as well as to anaphylactic shock) is the release of heparin into the circulation. This has not only been demonstrated for the shock caused by meconium embolism but has been confirmed as well for the "chemical" peptone shock. Second, if the release of heparin were a response of the organism to the shock itself, then there might be anticipated a similar release of heparin during the shock caused by fibrin embolism.[43] On the contrary, as previously found, there was no release of heparin in the shock of experimental fibrin embolism. Therefore, the possibility is not excluded that there may be a substance or substances in meconium which in some more specific way than by vascular occlusion, and possibly acting as a toxin, may mediate the release of heparin. No special studies were carried out to evaluate the presence or absence of such a substance in meconium but subclinical doses of meconium do not provoke release of heparin.[43]

Pulmonary vasospasm is significant in the dilatation of the right side of the heart (acute cor pulmonale) observed by Steiner and Lushbaugh. Conceivably, the vasopressor agent of platelets, serotonin, could be a mediator of such vasospasm.[47] Injection of platelet extracts by themselves, while causing extreme hypertension both systemic and pulmonary, did not alone cause acute cor pulmonale in the sense in which fibrin embolism and meconium embolism caused acute cor pulmonale.[45] That serotonin itself may nevertheless contribute to acute cor pulmonale is strongly suggested by the more minutely analyzed findings from refined methods of analysis.[25]

Coagulation of Drawn Venous Blood in Obstetrical Shock.—An interesting comparison between a kind of index of over-all coagulability of blood after thromboplastin infusion and after meconium infusion[43] is that: (1) In fibrin embolism, initiated by injection of thromboplastin into animals, venous blood will usually still coagulate and this with an approximately normal Lee-White coagulation time (sometimes accelerated, sometimes prolonged, varying with dosage and with time after injection). It should be emphasized that only under extreme experimental conditions is it possible to deplete the coagulation mechanism to such an extent that no further coagulation of venous blood will occur.[24, 27] (2) By contrast, in meconium embolism, the blood may fail to clot at all.[43]

This is comparable to the difference between the blood in cases of severe abruptio placentae and the blood in severe amniotic embolism. An approximate over-all difference clinically is that in abruptio placentae (with the exception of extreme cases[20, 24, 39]) venous blood will clot[13, 24, 37-47, 58] although forming perhaps only a frail clot[13, 20, 24, 39, 42, 58]; while in amniotic embolism, venous blood may fail to clot at all[7, 8, 28] even though there may still be fibrinogen in the blood.[28] Although Dooley and Leary[7] had added thrombin, yet in the light of the dog experiments cited here, this does not necessarily exclude the presence of fibrinogen. Indeed, it is not excluded by currently available data that, in some cases of shock of amniotic embolism, fibrinogen may remain in the blood in full measure.

The Problems of Intravascular Coagulation and Circulatory Obstruction in Abruptio.—Page[23] brought together a hypothesis from studies of intravascular coagulation caused by injection of decidual or placental extracts into experimental animals[34, 35] and from clinical problems of obstetrical hemorrhagic diathesis[5, 6, 16]; he proposed intravascular coagulation as a cause of defibrination in abruptio placentae. Fulton and Page[9] were able to demonstrate comparable defibrination experimentally. This not only confirmed an older finding of Mellanby, that defibrination of the blood can be caused by intravascular coagulation, but gave a direct application of this defibrination to a hitherto obscure problem of obstetrics. So far as is at present known, such active defibrination of the circulating blood as a result of intravascular coagulation is apparently, in all the fields of medicine, unique to late pregnancy, and is now widely accepted and supported as a mechanism of defibrination in abruptio placentae, even by some authors[29, 30] who had previously mentioned only fibrinolysis[57, 58] in discussing "afibrinogenemia" of abruptio placentae.

In abruptio placentae, this very defibrination provides a negative image of a possibly more important and preceding process, the occurrence of generalized intravascular coagulation.[37] Deductions based on such a "negative image" required further direct evidence (which soon became available)[39] because other interpretations concerning the fibrinopenia were possible, including the concept that the defibrination may have been the result of fibrinolysis[20, 58] rather than the result of intravascular coagulation.

More direct experimental evidence that problems of intravascular coagulation might be of importance to disorders of pregnancy was forthcoming when a kind of artificial abruptio placentae was induced in the pregnant rabbit.[36] Intravascular coagulation was implicated as a cause of sudden death and, in surviving animals, as a cause of focal lesions, including focal liver necrosis.[36]

An anatomic basis was discovered for a mechanism of autoextraction of decidual thromboplastin into the circulation during human abruptio placentae.[37] Intravascular fibrin deposits of a characteristic type were demonstrated.[39] Presumably acute cor pulmonale may develop as a result of the fibrin deposition during abruptio placentae.[47]

Fibrinolysis.—In 1949, Moloney, Egan, and Gorman[20] had reported marked fibrinolysis in drawn blood in association with abruptio placentae and interpreted the associated afibrinogenemia to be the result of fibrinolysis. Activation of the fibrinolysin of the blood may play an important role in the removal[39, 55] of the vascular occlusions of fibrin embolism. Conceivably, it may also play a role of variable intensity in contributing to or in bringing about defibrination.

From the only available direct observations of coagulation activities in a case of proved amniotic embolism recorded by Ratnoff and Vosburgh, and in contrast to the possible release of heparin suggested by the animal experiments just described, the question may be raised to what degree intravascular fibrinolysis may play a role in the failure of coagulation of amniotic embolism. In human blood, the conversion of the profibrinolysin of the blood to active fibrinolysin, during shock and/or during anoxia, seems to result in active and powerful fibrinolysis. Unfortunately, the fibrinolysin mechanism seems not to be as readily activated or as readily subject to investigation in laboratory animals. For this reason, solution of the problems of defibrination of late pregnancy in certain details may well depend upon continued and closer observations during the spontaneously occurring human disorders.

Presently available observations from the literature indicate that sometimes activation of fibrinolysin may be a significant process, contributing secondarily to a hemorrhagic diathesis both in severe amniotic embolism and in severe abruptio placentae. In abruptio placentae disseminated intravascular coagulation appears to be the primary cause of defibrination.

Fibrinolysis[20] may serve the beneficial function of early lysis of intravascular fibrin occlusions.[39] Thus the fibrinolysin mechanism may be a significant factor in rendering the obstetrical shock of abruptio placentae (but not the shock of amniotic embolism) a self-limiting process.[47]

The Problem of Intravascular Coagulation in Amniotic Embolism.—Recently, Reid, Weiner, and Roby[29, 56] have proposed that the concept of intravascular coagulation be applied not only to abruptio placentae[39] but also to the problem of maternal amniotic embolism. In support of priority for this interpretation, these investigators[30, 57] called attention to a report concerning an interpretation of an "antihemophilic factor" in amniotic fluid. This apparent "antihemophilic" activity of amniotic fluid they have interpreted as being identical with (tissue) thromboplastin activity.[29, 31]

A decidual toxin and a placental toxin,[34] like a brain tissue toxin,[55] have been identified as tissue thromboplastin[17, 35]; the identification rests on the basis of sedimentation properties, biochemical properties of initiation of coagulation, and susceptibility to enzymatic and to physical and chemical inactivations.[35] It had also been shown by similar determinations that there is a small although definite activity of tissue thromboplastin in amniotic fluid; the quantity is so small as to be of questionable significance to amniotic embolism.[37]

To the present time, conclusive evidence is still lacking that disseminated intravascular coagulation occurs in amniotic embolism. Even allowing that both abruptio placentae and amniotic embolism might occur in the same patient, yet no "fibrin plugs" or other pathologic evidence of fibrin embolism during amniotic embolism, or coexisting with amniotic embolism, have been reported.[43] In a recent survey[19] from a pathologic museum with a wide spectrum of cases, including just the desired kinds of anatomic pathologic specimens, no mention is made of intravascular fibrin deposition in amniotic embolism.

Reid, Weiner, and Roby[29] have made a presumptive diagnosis of intravascular coagulation in a patient for whom they entered a clinical diagnosis of amniotic fluid embolism. The diagnosis of defibrination was based on an observa-

tion of fibrinopenia as low as 24 mg. per cent. The diagnosis of amniotic embolism was presumptive and apparently by exclusion, on the basis that abruptio placentae was not demonstrated. The patient survived and it was never possible to establish the diagnosis of amniotic embolism.[52, 53] It would seem that another interpretation of the case might be possible. When I investigated similar (not reported) cases of acute hemorrhagic diathesis with fibrinopenia, detected soon after labor and delivery, a presumptive diagnosis of intrapartum abruptio placentae seemed to offer the simplest interpretation. The possibility that intrapartum abruptio may occur has been considered previously.[40]

It can be calculated, and is supported by comparison with experimental infusions, that because of the low concentration of thromboplastin inherently present in amniotic fluid, an unusually voluminous and sudden infusion of amniotic fluid into the maternal circulation would be required in human pregnancy to cause significant intravascular coagulation. Hence, as has been pointed out,[43] it would be necessary to invoke an accompanying hypothesis of some kind of autoextraction of thromboplastin while the amniotic fluid passes into the maternal circulation. Reid, Weiner, and Roby have made such a hypothesis recently.[32] The suggested autoextraction was different from the autoextraction in abruptio placentae in that amniotic fluid rather than blood[37, 40, 42] acts as the extracting medium. The pathway of flow of the amniotic fluid into the maternal circulation was essentially that suggested by Schenken, Slaughter, and DeMay,[33] namely, by dissection of amniotic fluid behind the membranes to the placental margin and to the marginal venous plexus. This would provide an autoextraction, not from the decidua basalis as in abruptio, but possibly from the decidua over the membranes (a diagram of the hypothetical autoextraction is presented elsewhere[44]). Unlike the observations from abruptio placentae, direct or indirect evidence for any massive autoextraction of decidual thromboplastin during amniotic embolism is still lacking.

In the light of the experimental results presented here and if experimental meconim embolism may be properly considered as an equivalent of at least one kind of amniotic fluid embolism, then it is unnecessary to postulate that the pathologic process of circulatory obstruction after amniotic fluid embolism is largely one of intravascular coagulation. Such a hypothesis is all the more difficult to substantiate in the face of an already adequate concept, namely, that of disseminated pulmonary embolism of amniotic debris.[52]

Obstetric Shock and Inhibition of Coagulation.—The experiments cited here establish that heparin is released during the shock of experimental meconium embolism in dogs. During the shock of fibrin embolism no comparable release of heparin was found. In direct contrast, only minor changes of a "true" antithrombin activity, in the sense of a thrombin inactivator, were found in relation to the shock of fibrin embolism; no change of this activity at all was found during the shock of meconium embolism.

During fibrin embolism, quite aside from the inhibitors of coagulation, prolongation of the coagulation time could be accounted for by depletion of one[14] or more of the accelerators of coagulation, if indeed not by depletion of the ultimately concerned substrate of coagulation, fibrinogen. A similar accounting, however, is not as readily accomplished by the present experiments for the apparent "thrombin-inhibitory activity" observed by Ratnoff and Conley.[27] After injection of tissue extracts, Ratnoff and Conley mixed a small amount of the experimental animal's blood with thrombin or with thrombin and normal plasma. They reported an appreciable over-all thrombin-inhibitory effect that developed during and after injection of thromboplastin. The discrepancy with the present experimental results may be, however, more apparent than real. Not only was a different technique of assay used, but the dose of thromboplastin was

probably much larger; they gave a prolonged infusion over an interval of two hours. By contrast, the dogs for the antithrombin assays for the present studies received only a single injection or repeated single injections (Table VII).

Neither was release of heparin demonstrated during the shock of human abruptio placentae.

The apparent small decrease of antithrombin activity after injection of thromboplastin into dogs, and after abruptio placentae, became apparent after a lag phase of an hour or more. This would lead to the suggestion of further investigations to account for the apparent lag phase, perhaps in terms of a compensating activation of an accelerator of antithrombin activity.[48] Studies in these directions have not been undertaken.

At the level of investigation of the biochemist there is known to be a partial decrease of antithrombin activity in serum, as compared with that in its parent plasma.[49] After injection of sufficiently large doses of thromboplastin intravascularly, different components of the coagulation mechanism are used up.[9, 14, 15, 39] The circulating blood under these conditions may be interpreted as essentially a suspension of formed elements, not in plasma, but in serum (Table I). In any event, defective coagulation during abruptio placentae, due to an increased over-all antithrombin activity, seems likely to be of small importance by comparison with the depletion of fibrinogen and of the general coagulation mechanism itself.

Because of the release of heparin into the blood, found during the shock of experimental meconium embolism, it is tempting to speculate as to whether a similar release of heparin may occur in maternal amniotic embolism. If release of heparin is found in amniotic embolism, this would be the first demonstration of release of heparin into the circulation in a human disorder.

Ratnoff and Vosburgh reported an increased thrombin-inhibitory activity in their patient with amniotic embolism. Their assay is valuable because it detects an over-all type of thrombin inhibition. There is no way to determine whether the inhibitor in their patient may have been heparin, or to what degree it may have been the result of an inhibitor in the sense of a thrombin inactivator, and their pioneer investigations make evident the need for further specific measurements.

Therapy.—Concerning the development of a hemorrhagic diathesis in obstetric shock, it is pertinent to note that treatment of the patient may be successful quite independently of treatment of the coagulation defect. The coagulation defect may become of importance clinically only if a latent hemorrhagic diathesis becomes a manifest hemorrhagic diathesis.[37, 50]

Animals with experimental defibrination or with experimental induction of heparin release do not usually have hemorrhagic tendencies of serious proportions unless there is superimposed traumatic laceration or surgical incision. In experimental animals, usually no artificial restoration of the coagulation mechanism is necessary because natural processes soon correct the latent tendency toward a hemorrhagic diathesis.

Similarly, in abruptio placentae, except in extreme cases, artificial restoration of the coagulation mechanism is usually not indicated as a separate procedure of itself. Hemorrhage may well occur if defibrination persists during the time of trauma, of surgery, or of delivery. Then, because of blood loss, whole-blood transfusion may be needed. As pointed out by Page, Fulton, and Glendening[24] and others,[39, 50] blood may be adequate not only to restore blood volume, but at the same time to restore the blood coagulation mechanism adequately for hemostasis. As yet, the importance of platelets as contrasted with the plasma components of hemostasis has hardly been considered.

It is important to keep in mind that excessive infusion or transfusion in abruptio placentae may contribute to a fatal outcome,[16, 39] especially because of the hazard of possible coexistence, of recent acute cor pulmonale.[47]

In amniotic embolism, excessive infusion or transfusion may be even more hazardous than in fibrin embolism. One cannot do other than wonder as to the degree of hypervolemia when a patient is given 20 L. of fluid[28] (an equivalent to almost four complete exchanges of the total circulatory volume), much of it whole blood, without an accounting of total blood loss. Overloading of the circulation, especially with a heart perhaps already in, or recently in, acute cor pulmonale from the amniotic embolism itself, may have occurred. This possibility is all the more pertinent since Steiner, Lushbaugh, and Frank[53] have observed that, without any hemorrhage, the obstetrical shock (with probable acute dilatation of the right side of the heart) may be fatal by itself.

As yet neither abruptio placentae nor amniotic embolism can be predicted precisely. From the results of the present investigation, there seems to be no place for the use of protamine or of toluidine blue in the treatment of a hemorrhagic diathesis of abruptio placentae. These agents also inhibit coagulation of themselves, and could be expected only to aggravate the hemorrhagic tendency. Also, at present, it is uncertain whether either of these substances would be useful against the hemorrhagic tendency of amniotic embolism—the hazard of "overtitration" is considerable.

In summary, in abruptio placentae but especially in amniotic embolism, it is necessary to refrain from overloading the circulation which may already have become embarrassed by a tendency to right heart failure. Usually, the potential hemorrhagic diathesis of abruptio placentae may be prevented from becoming a manifest hemorrhagic diathesis, if prompt termination of the pregnancy is carried out as an obstetric emergency.

Summary

The obstetric shock of amniotic embolism was interpreted by its discoverers as being due to pulmonary embolism of amniotic debris. Similar obstetric shock which occurs during abruptio placentae is interpreted as being due to pulmonary vascular occlusions caused by fibrin deposition. Important as fibrin deposition may be in abruptio placentae, as yet no evidence has been presented indicating that fibrin coagulation contributes importantly to the circulatory embarrassment of amniotic embolism.

Shock was induced in dogs by causing experimental meconium embolism. The circulating blood became incoagulable. The plasma components of coagulation were not used up; fibrinogen, prothrombin, and accelerator globulin (i.e., labile factor, or Factor V) remained in full strength. Heparin was present in the circulating blood. There was no increase or decrease of antithrombin activity other than the antithrombin activity of the heparin.

Shock was also caused by inducing fibrin embolism by injection of crude extracts of tissue thromboplastin. Coagulation then also became defective but the mechanism was quite different in that the components of coagulation were essentially used up. Heparin was not present. There was no significant change of true antithrombin activity, in the sense of an inactivator of thrombin, at the time of the acute episode. Essentially, the circulating "blood" had become a suspension of formed elements, not in plasma, but in serum.

In blood from maternity patients with abruptio placentae, the changes were similar to those in dogs after injection of thromboplastin. No sample of plasma was available from a case of maternal amniotic embolism. The question is raised whether heparin will be found in blood from cases of human amniotic embolism as it was in blood from experimental meconium embolism in dogs, and

whether the "thrombin-inhibitory" activity in a case of amniotic embolism reported in the literature was due to a true antithrombin or, by comparison with the experiments previously described, may have been due to heparin. (A demonstration of heparin, even in postmortem blood, would be significant.) Since heparin has yet to be demonstrated by a specific method in any human disorder or in extracts of any human tissue, however, it would be premature to conclude that heparin is likely to be found in maternal amniotic embolism.

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THE USE OF CHLORPROMAZINE* IN THE OBSTETRIC PATIENT: A PRELIMINARY REPORT

I. In the Treatment of Nausea and Vomiting of Pregnancy

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PREGNANCY is such a natural fulfillment of womanly function that many women feel and look their best at this time. The eye has a sparkle, the cheek a flush that has earned the term, and rightly, of "the bloom of pregnancy." Strange, then, that many gravid women are not so fortunate and some time between the second and fifth week of their pregnancy begin to suffer from nausea and vomiting. Usually, these symptoms occur only in the morning and involve emesis of the morning meal or of the accumulated gastric secretion of the night before. The rest of the day the patient feels relatively well. This rather mild affliction is well tolerated by the pregnant woman; it may, in fact, be the first symptom that suggests pregnancy to her.

More annoying than morning vomiting is the condition of persistent nausea which makes the odor or even the suggestion of food intolerable. In this condition, vomiting is a relief to the patient. Of greater import and more distressing to the patient is the occurrence of episodes of vomiting during the day and, less frequently, the really serious form designated "hyperemesis gravidarum" in which neither food nor liquid is tolerated. It is this latter condition which, if untreated, or treated too late, may prove fatal.

Much is surmised regarding the etiology of nausea and vomiting of pregnancy, and much stress is laid on the fact that there is a disturbance of the patient's sensorium. Regardless of where the cause lies, persistent nausea and vomiting induce changes in the electrolyte and vitamin balance of the individual that require corrective treatment if the organism is not to suffer. This is true regardless of whether the basic etiology of the syndrome is organic or psychic.

In view of the fact that the specific cause of the nausea and vomiting of pregnancy is unknown, it is not surprising to find that treatments for relieving the syndrome are many and varied, ranging from the use of sedatives and vitamins to psychotherapy and hypnosis. Although many treatments for mild nausea and vomiting have been claimed beneficial, physicians are becoming increasingly aware that effective treatment for the more severe symptoms depends,

*A new phenothiazine derivative, with the chemical name of 10-(3-dimethylaminopropyl)-2-chlorphenothiazine hydrochloride, the generic name of chlorpromazine and the trade name of Thorazine (S. K. F.).

to a great extent, in restoring the patient's fluid, electrolyte, and vitamin balance. These objectives are usually accomplished by intravenous therapy or by duodenal tube feedings. The purpose of the present study is to evaluate a new compound which, it was hoped, would provide by means of a single medication a simple, effective treatment for both the nausea and vomiting of pregnancy, and hyperemesis gravidarum.

Method

Medication.—Chlorpromazine,* the medication chosen for this study, is a new phenothiazine derivative with marked action on the central nervous system. Several animal and clinical studies have demonstrated, among other things, that the compound is effective in suppressing disease and drug induced emesis[1, 2] and that it has no ill effects on pregnant mammals or their progency.[3]

Patients.—The study was conducted on 158 private patients selected from the practices of the obstetrical staff at the Chicago Wesley Memorial Hospital (Fig. 1). The patients furnished a typical cross section of an urban group, no more and no less neurotic than any other segment of the population. They were, in the main, economically stable women accustomed to doing their own housework who had, therefore, a real incentive to achieve as quick a recovery as possible. Of these, 141 patients suffered from nausea and/or vomiting (97 from both symptoms, 44 from nausea alone); 17 patients suffered from hyperemesis gravidarum.

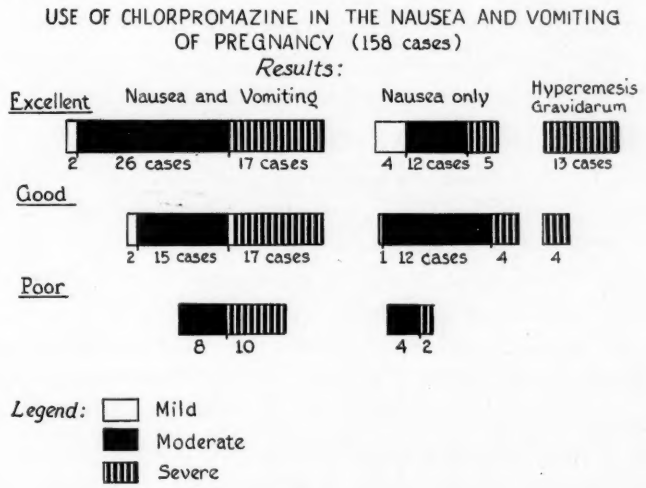

Fig. 1.

The 17 patients with hyperemesis gravidarum ranged in age from 18 to 35 years (average age, 24.9); 8 of them were primigravid. At the time of hospitalization 6 of the patients had been pregnant for two months; 5 for two and a half months; 3 for three months; 2 for three and a half months; and 1 for four months. The duration of symptoms prior to hospitalization varied from three to four days of intensive vomiting to—in one patient—a chronic condition of three months' duration. The majority of patients had been previously treated with sedatives, dimenhydrinate, and/or vitamins.

Dose.—Considerable reaction in individual response made it necessary to adjust the dose to the patient's reaction and to the severity of the symptoms.

*Thorazine, Smith, Kline & French Laboratories.

Patients suffering from nausea and/or vomiting were started on from 10 to 50 mg. three or four times a day. We have found that 50 mg. at bedtime and 25 mg. late in the morning is well tolerated by most patients. Those who were unable to tolerate medication orally were given 25 to 50 mg. intramuscularly twice a day or 25 mg. four times a day; patients were then given oral sustaining doses ranging from 10 to 50 mg. three times a day.

The most frequent initial dose for patients with hyperemesis gravidarum was 25 to 50 mg. intramuscularly two or three times a day. Later they were sustained on oral doses of from 10 to 50 mg. three times a day.

Of the 141 patients who suffered from nausea and/or vomiting, 117 (83 per cent) were significantly benefited by chloropromazine. Response to medication usually occurred within one or two days. Of the 97 of these patients who suffered from both symptoms, 79 (81 per cent) were helped by the medication (45 experienced a complete cessation of symptoms); 18 (19 per cent) were not. Of the 44 patients who suffered from nausea only, 38 (86 per cent) were helped by the medication (21 experienced a complete cessation of nausea); 6 (14 per cent) were not. The detailed results (showing the degree of relief obtained and the severity of the symptoms) are given in Tables I and II.

TABLE I. RESULTS IN PATIENTS WITH NAUSEA AND VOMITING

DEGREE OF RELIEF		NUMBER OF PATIENTS WHOSE SYMPTOMS WERE			TOTAL
NAUSEA	VOMITING	MILD	MODERATE	SEVERE	
Complete	Complete	2	26	17	45
Partial	Complete	0	5	7	12
None	Complete	0	1	1	2
Partial	Partial	2	9	9	20
None	None	0	8	10	18

TABLE II. RESULTS IN PATIENTS WITH NAUSEA ONLY

DEGREE OF RELIEF	NUMBER OF PATIENTS WHOSE NAUSEA WAS			TOTAL
	MILD	MODERATE	SEVERE	
Complete	4	12	5	21
Partial	1	12	4	17
None	0	4	2	6

All of the 17 patients with hyperemesis gravidarum were benefited by chlorpromazine. Thirteen of them made an excellent recovery (a complete and rapidly achieved cessation of symptoms); 4 made a good recovery (an almost complete cessation of symptoms). None of these patients aborted; the 7 babies that have been delivered at the time of this writing are all living and healthy, and the pregnancies in the 10 as yet undelivered patients are progressing normally. The length of time these patients stayed in the hospital varied from two to ten days (average, 4.2 days).

Side Effects.—Of the 141 patients treated for nausea and/or vomiting, 63 complained of drowsiness (5 of these discontinued the medication); 6 complained of dizziness; 2 of weakness; 2 of headache; and 5 of one of the following: lump in throat, mouth lesions, puckered mouth, heartburn, indigestion. All of these effects, except drowsiness, were transient. Drowsiness was eliminated in many patients by lowering the dose or by giving d-amphetamine sulfate in addition to the medication. The few patients who suffered from faintness did so after the intramuscular administration of the drug; this effect could be controlled by having the patient remain recumbent for several minutes after the injection. In order to avoid possible tissue reactions, intramuscular injection should be given deeply. The chief side effect, drowsiness, was therapeutically advantageous in treating severe symptoms.

Comment

It appears from this study that chlorpromazine not only exerts an effective action on the vomiting mechanism but also that it does this without greatly affecting any other bodily function. Its side effects are usually mild and transitory, although the drowsiness produced by the drug can be annoying to the ambulatory patient. Chlorpromazine acts promptly (sometimes within an hour or so after administration) and is effective both orally and intramuscularly. It should be stressed, however, that the very effectiveness of the drug should give rise to a degree of caution in its use; the cause of nausea and vomiting should be quite clear before the drug is administered in order to prevent the masking of a serious systemic disorder.

Summary and Conclusions

One hundred fifty-eight pregnant women suffering either from nausea and/or vomiting (141 patients) or hyperemesis gravidarum (17 patients) were treated with chlorpromazine, a new phenothiazine derivative. The drug was of benefit in 117 (83 per cent) of the 141 patients suffering from nausea and/or vomiting; in all of the 17 patients with hyperemesis gravidarum. Response usually occurred within one or two days. The most important side effect was drowsiness, a reaction which was therapeutically valuable in treating more severe symptoms. Where it was desirable to combat drowsiness, dextroamphetamine sulfate, in 5 to 10 mg. dosage, was effective. The data obtained from this study seem to warrant the following conclusions:

1. Chlorpromazine appears to be an effective drug for the treatment of nausea and vomiting of pregnancy. Good-to-excellent results can be expected in a significant majority of patients.
2. It appears effective in treating hyperemesis gravidarum; complete, or almost complete, cessation of symptoms occurs in from one to five days.
3. It does not usually cause side effects serious enough to require discontinuance of the medication.
4. It is effective both orally and intramuscularly; severe cases respond best to intramuscular administration.
5. It does not have a harmful effect on mother or child.

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THE USE OF CHLORPROMAZINE* IN THE OBSTETRIC PATIENT: A PRELIMINARY REPORT

II. The Treatment of Nausea and Vomiting of Labor and Delivery With Special Reference to the Effects on Analgesia and Anesthesia and on the Newborn

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NAUSEA and vomiting in the obstetric patient in labor are common. The emesis basin on the bedside table of the parturient is part of the armamentarium of the labor-room nurse. Vomiting has been attributed to medication, to the accompanying alimentary stasis, and has been noted as a signal of the onset of the expulsive stage of labor. Occurring before the administration of anesthesia, vomiting cannot seriously jeopardize the conscious patient. It is in the anesthetized unconscious patient that the danger lies. Serious illness and death from aspiration are still factors in the morbidity and mortality of the parturient.

The onset of labor is usually unpredictable so that few patients enter the hospital adequately prepared. It is not uncommon to find food ingested many hours before admission still present in the stomach and consequently an anesthetic hazard. Preanesthetic gastric lavage is a recognized solution. It is, however, so unpleasant for all concerned that it is seldom utilized. Members of the anesthetic staff had administered chlorpromazine in the past year as a preanesthetic medicament to the surgical patient. They noted a hypnotic and sedative action on the central nervous system, a potentiating effect on narcotics, analgesics, and anesthetics, and confirmed its antiemetic properties. In selected cases chlorpromazine was administered to the postoperative patient in whom it was found to reduce nausea and vomiting and to allay anxiety; it enhanced the effects and reduced the dosage of analgesic drugs. It was therefore postulated that the dangers of aspiration in induction of anesthesia, and in the unconscious patient in the immediate postpartum period would be reduced by the administration of chlorpromazine as a preanesthetic medication. Accordingly, a plan of procedure was instituted to evaluate the effects of chlorpromazine on the parturient during the first and second stages of labor, and in the immediate postpartum period.

*A new phenothiazine derivative, with the chemical name of 10-(3-dimethylaminopropyl)-2-chlorphenothiazine hydrochloride, the generic name of chlorpromazine and the trade name of Thorazine (S. K. F.).

Method and Procedure

Chlorpromazine was administered to all obstetric patients except those actively bleeding. Toxemic patients were included in the study. All patients who were in active labor received 25 mg. of the drug intramuscularly as soon as active labor was established, and every 4 to 6 hours during labor, depending upon the existing state of sedation. Those patients who were admitted to the hospital in active labor and ready to be delivered received 25 mg. intramuscularly immediately upon admission. Pertinent data were recorded on study forms by the obstetrical resident during labor and the postoperative period and by the anesthesiologist during delivery. The doses of analgesics used during labor were reduced to one-half the dose usually given without chlorpromazine because of its potentiating effects. This did not affect the dosage of scopolamine.

There were 214 patients studied in this preliminary report: 114 parturients were treated with chlorpromazine; 100 were untreated and served as a control group. Of the treated group, 64 were multiparas, 50 were primiparas. There was no selection of cases other than women who were in active labor. There were 101 vertex presentations (6 posterior positions); 3 breech presentations; 10 cesarean sections; 7 cases of toxemias, and 1 transverse arrest.

The medication in the treated group consisted of chlorpromazine alone or in combination with analgesics, hypnotics, atropine, or scopolamine (Table I).

Dosage.—The average dose of chlorpromazine was 25 mg.; the largest was 100 mg. in 4 divided doses. The average dose of scopolamine hydrochloride was 0.4 mg.; the largest 0.8 mg. given in 2 divided doses. The average dose of Demerol was 50 mg.; the largest 175 mg. in 3 divided doses. The method of administration was intramuscular in the majority of cases (106); the remainder (8 cases) received the drug intravenously.

TABLE I. USE OF CHLORPROMAZINE IN 114 OBSTETRICAL CASES

Number of Cases.—			
Primiparas	64		
Multiparas	50		
Vertex presentation		101*	
Breech presentation		3	
Cesarean section		10	
Toxemia		7	
Transverse arrest		1	
Medications.—			
Chlorpromazine alone			11
Chlorpromazine + meperidine			14
Chlorpromazine + atropine			6
Chlorpromazine + scopolamine			3
Chlorpromazine + meperidine + scopolamine			72
Other combinations included chlorpromazine with Seconal, Amytal, meperidine and atropine, and morphine and scopolamine.			
Method of Administration.—			
Intramuscular	106		
Intravenous	8		
Dosage.—			
	AVERAGE	LARGEST DOSE	
Chlorpromazine	25 mg.	100 mg. (in 4 divided doses)	
Scopolamine	0.4 mg.	0.8 mg. (in 2 divided doses)	
Meperidine	50 mg.	175.0 mg. (in 3 doses)	

*Six of these in posterior position.

The anesthesia for delivery (in the treated group) consisted of the inhalation method in 75 cases; of these cyclopropane was administered to 70 patients; ethylene and nitrous oxide to 5 patients. Spinal anesthesia with heavy solution of Nupercaine was the method used in 24 patients, and pudendal block in 9. Six patients had no anesthesia for delivery (Table II).

TABLE II. METHODS AND AGENTS OF ANESTHESIA

METHOD	NO. OF CASES	AGENT
Spinal block	24	Nupercaine
Pudendal block	9	Xylocaine
Inhalation	70	Cyclopropane
	5	Ethylene + nitrous oxide
No anesthesia	6	

Nausea and Vomiting of Labor and Delivery.—Fig. 1 is a summary of the incidence of nausea and vomiting of labor and delivery. In the chlorpromazine group, in the first stage of labor, 3 patients (2.6 per cent) vomited once or twice; 3 patients (2.6 per cent) were nauseated only; 1 patient (0.9 per cent) vomited more than 3 times. In the second stage of labor 3 patients (2.6 per cent) vomited once or twice after receiving chlorpromazine. In the third stage 7 patients (6 per cent) vomited one or two times. In the third stage 7 patients (6 per cent) vomited one or two times. Thus, 11.4 per cent had moderate emesis (once or twice) and the total incidence of symptoms was 16 per cent.

In the control group the total incidence of symptoms was 27 per cent, 13 per cent occurring in the first stage, 5 per cent in the second stage, and 9 per cent in the third stage of labor. The intensity of symptoms in the control group was greater, 7 per cent of the patients vomiting more than three times.

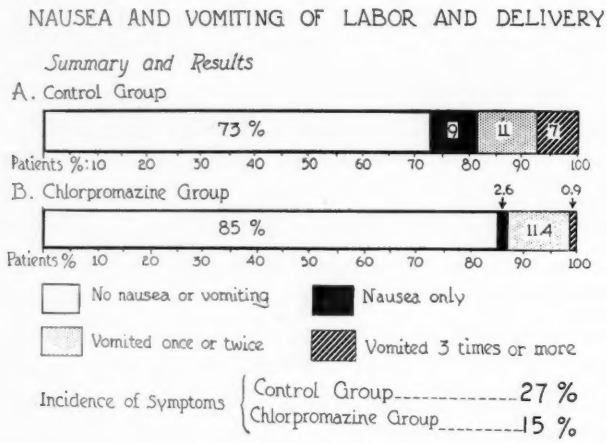

Fig. 1.

Other Observations

Analgesic, Hypnotic and Sedative Effects (Table III).—Chlorpromazine alone revealed good hypnotic effects; 8 of 11 patients who received this drug alone slept between pains, but responded to stimuli, and one was awake but comfortable between pains. In one patient the drug was ineffective, and in one there was no information.

All combinations of chlorpromazine and analgesics or hypnotics with or without scopolamine were more effective in hypnotic sedative action than previously attained with the latter drugs alone. A good response occurred in 77 of 98 observed cases; that is, the women dozed or slept between pains but responded readily to varying degrees of stimuli. A poor response, consisting of disorientation, restlessness, or wildness was found in 7 patients. There was no observable reaction to the drug in 14 patients.

The degree of sedation and hypnosis varied greatly (Table IV); some patients were quiet but awake; the majority dozed off between contractions, but responded readily to stimuli; a few could be aroused only slightly even during uterine contractions. Amnesia was present in a few patients. Some patients described the state induced by the drug as pleasant, restful, and relaxing. In many a "medical prefrontal lobotomy" effect was observed—a torpor, a mask-like facial expression, a quiet phlegmatic acceptance of pain.

The height of analgesic, sedative, and hypnotic effect of chlorpromazine occurred 1¼ to 2 hours after an intramuscular injection.

Effect on Duration of Labor.—Labor seemed to be accelerated in some patients who were treated with chlorpromazine. In others there was no change. Occasionally, however, the drug appeared to reduce the strength of uterine contractions in primagravidas. In 3 patients the force of labor pains was definitely diminished and the strength of active abdominal muscular pressure in the expulsion was also reduced and labor prolonged. Two patients had inertia following delivery, with moderate to excessive bleeding. In spite of these variations the duration of labor in the chlorpromazine and in the control groups was found to be similar. In the chlorpromazine series 56 per cent of the patients had a first stage of labor which lasted less than 6 hours; 23 per cent between 6 and 12 hours; and 21 per cent between 12 and 26 hours. In the control series 56 per cent of the patients had less than 6 hours of first stage labor; 31 per cent had 6 to 12 hours; 11 per cent had 12 to 24 hours; and 2 per cent over 24 hours (Fig. 2).

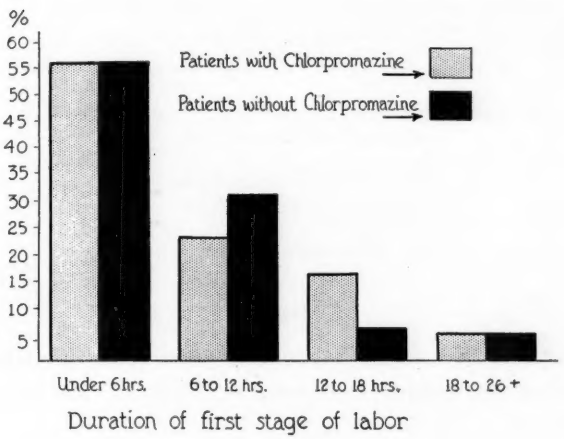

Fig. 2.

There was no significant effect of the drug on the newborn. In the control group 11 of 100 infants had delayed respiration (7 requiring resuscitation). In the chlorpromazine group 10 of the 114 newborns had delayed respiration (3 requiring resuscitation). There were no maternal or fetal deaths in the two series studied.

Side Effects.—Side effects noted in the treated series were flushing (observed in 14 patients), dry mouth (11), and flaccidity (2).

The average drop in blood pressure in the chlorpromazine-treated series was 10 points in systolic and diastolic readings. The greatest hypotension occurred immediately following the induction of spinal anesthesia. The next largest drop of blood pressure was observed in the toxemic hypertensive patients. It was often difficult to raise the resultant low blood pressure, even with large doses of sympathomimetic drugs. One toxemic patient, who had been given 50 mg. of

chlorpromazine intravenously, required a continuous infusion of norepinephrine to raise the blood pressure to normal from shock level.

The effect on body temperature was not significant or constant. The temperature was reduced about 0.5 to 1° F. in most cases.

TABLE III. HYPNOTIC, SEDATIVE, AND ANALGESIC EFFECTS

11 patients (10%) received chlorpromazine alone. Of these:	
8 slept between pains but responded to stimuli	
1 awake but comfortable between pains	
1 ineffective	
1 no information	
72 patients (63%) received chlorpromazine, meperidine, and scopolamine. Of these:	
34 were in deep sleep but responded to pains and stimuli	
16 awake but comfortable	
9 no effect because medication was given too late or too early	
3 unconscious, not responding to stimuli	
3 disoriented, wild, and "scopy"	
7 no information	
15 patients (13%) received chlorpromazine and meperidine. Of these:	
8 slept between pains but responded to stimuli	
3 awake but comfortable	
4 no effect	
6 patients (5%) received chlorpromazine and atropine. Of these:	
1 slept between pains	
3 awake but comfortable	
2 no information	
3 patients (2.6%) received chlorpromazin and morphine. Of these:	
2 slept between pains and responded to stimuli	
1 was unconscious, did not respond to stimuli	

TABLE IV. HYPNOTIC, SEDATIVE, AND ANALGESIC EFFECTS OF MEDICATION (CHLORPROMAZINE GROUP)

I	Deep sleep between pains
II	Awake but comfortable
III	Ineffective
IV	No information

Comment

From observations of the first 114 obstetric patients who received chlorpromazine, the following dosage and time schedule of analgesic drugs are suggested:

I. Chlorpromazine 25 mg.
Meperidine 50 mg.
Scopolamine 0.4 mg.
} Intramuscularly, 2 to 4 hours before delivery

II. If delivery will occur within one hour, ½ the chlorpromazine dose alone is given intravenously (10 to 12 mg. diluted to 5 c.c. and administered very slowly.

III. Primiparas: The first dose of chlorpromazine, 25 mg., Meperidine, 50 mg., and scopolamine, 0.4 mg., is given intramuscularly, when the cervix is 4 to 5 cm. dilated, or before, if strong labor is established. This dosage and combination of drugs is repeated in 3 to 5 hours if labor is long and more sedation is required.

IV. Multiparas: The same combination and dosage of drugs are given intramuscularly when the multipara is in strong labor and the cervix is 3 to 4 cm. dilated. This may be repeated in 3 to 5 hours if necessary to assure a quiet, somnolent patient.

Preliminary Conclusions

1. Chlorpromazine appears to reduce the incidence and severity of nausea and vomiting markedly in all three stages of labor.

2. Chlorpromazine appears to potentiate analgesics, reducing doses by approximately one-half. It has a sedative and hypnotic action per se.

3. Chlorpromazine does not appear to exert any significant effect on the duration of labor; however, the strength of uterine contractions is occasionally reduced in the primigravida.

4. It produces a "medical prefrontal lobotomy" effect on many patients, a quiet phlegmatic acceptance of pain.

5. It exerts a hypotensive effect with an average drop of 10 points in systolic and diastolic blood pressure.

6. No harmful effects of the drug on mother or child have been observed in the present small series.

THE THIRD-DEGREE LACERATION IN MODERN OBSTETRICS

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THE last twenty years have seen the advent of "operative obstetrics."[1] An entirely new concept has thus replaced the "hands off" policy of the older obstetricians, particularly in the management of the second stage of labor. The frequent use of episiotomies and forceps has contributed to hastening the delivery process for the mutual benefit of the mother and her infant. Operative obstetrics are commonly practiced today in the United States where most deliveries are performed in hospitals and midwifery is practically nonexistent.

Diligent intervention by the obstetrician to terminate the second stage of labor has resulted in fewer traumatic sequelae. One of the reasons for this, certainly, as has been pointed out by Eastman,[2] has to do with the better facilities available to the physician of our era, working in a well-equipped hospital. These facilities were lacking to our predecessors when home deliveries were the rule rather than the exception. On the other hand, the lacerations and fistulas that the older obstetricians saw had usually occurred following long pounding of the presenting part on the perineum. They were often found in overstretched, crushed, and even devitalized tissues.[3] In contrast to this, the episiotomy extensions and lacerations that we see today are fresh surgical wounds in undamaged tissues with unimpaired blood supply and should therefore heal well by first intention. It has, for instance, been pointed out recently[4] that vesicovaginal fistulas can be repaired easily immediately following delivery. This is contrary to the data found in most textbooks of gynecology[5] where the advice is given to wait at least six weeks before attempting surgical closure of the fistula.

It had been our impression that difficulties were seldom experienced postpartum by patients who had sustained a complete tear through the anal sphincter and rectal mucosa at the time of delivery—the type of perineal tear commonly referred to as "third-degree laceration" in the literature. In this study, we proposed to review the third-degree lacerations which occurred at Emanuel Hospital within the last five years in an attempt to re-evaluate the importance and treatment of that type of birth trauma in modern obstetrics.

Thirty-seven third-degree lacerations occurred during that period of time. They were encountered 26 times in 6,077 median episiotomies, an incidence of 0.42 per cent, and 11 times in 12,715 mediolateral episiotomies, an incidence of 0.08 per cent.

Table II shows the parity of the patients in the series. Eighteen of these patients were primiparas. Thirteen were para ii, five were para iii, and one was para iv.

TABLE I. PERIOD FROM 1949 TO 1953 (INCLUSIVE)

		PER CENT
Total deliveries	23,248	
Third-degree lacerations	37	0.15
Median episiotomies	6,077	
Third-degree lacerations	26	0.42
Mediolateral episiotomies	12,715	
Third-degree lacerations	11	0.08

TABLE II. PARITY

Para i	18
Para ii	13
Para iii	5
Para iv	1

Three of these lacerations were associated with spontaneous deliveries, 28 with elective low forceps, and 5 with midforceps rotations and extractions. One laceration was the result of a difficult breech delivery (Table III).

TABLE III. TYPE OF DELIVERY

Spontaneous	3
Elective low forceps	28
Midforceps rotations and extractions	5
Breech	1

Spinal anesthesia was used 19 times, general anesthesia 17 times. Pudendal block anesthesia was used once.

TABLE IV. TYPE OF ANESTHESIA

Spinal anesthesia	19
General anesthesia	17
Pudendal block	1

Since more patients are delivered under general anesthesia than under spinal anesthesia in this hospital, those figures tend to show that third-degree lacerations are more frequent when spinal anesthesia is used. This conclusion, however, will have to await the results of comparison of two larger homogeneous series.

The average duration of hospital stay for the group was 7 days. This compares closely with the usual hospitalization period in uncomplicated obstetrical cases.

Sixteen infants in the series weighed more than 8 pounds, the largest 9 pounds, 12 ounces. This complication, however, is far from being always associated with large infants, since in 8 deliveries the infant weighed less than 7 pounds, the smallest of these weighing 5 pounds, 12 ounces.

Mention of tenderness in the area of the episiotomy was recorded 5 times in the nurses' notes. The tenderness was associated with mediolateral episiotomies in 4 cases, while it was found to be due to a hematoma in one instance where a median episiotomy had been used.

All the patients reported upon in this series were private patients. Six of the 37 were delivered by general practitioners, the rest by specialists. The ratio of deliveries by general practitioners to deliveries by specialists in this hospital being one to two, the figures seem to prove that the general practitioners are more careful in avoiding third-degree lacerations.

There was no agreement on the postpartum care of the 37 patients. Prophylactic antibiotics were used in two-thirds of the cases, either singly or in combinations. These were: penicillin, streptomycin, Aureomycin, Chloromycetin, Terramycin, and lately Neomycin. Sulfonamides, particularly Sulfasuxidine and Sulfathalidine, were also given following the laceration. Sulfathiazole crystals were sprayed into the wound twice. It is hard to evaluate the efficacy of the various antibiotics since there was no febrile morbidity in the series. It is interesting to note that most of the cases in which no antibiotics were used—one-third of the cases in the series—are recent, showing that the tendency at present is to do away with prophylactic antibiotics in the treatment of these lacerations. The lack of morbidity in this series is remarkable and conflicts with that reported earlier in the literature.[6] We would like again, however, to repeat that we are no longer dealing today with the same type of birth injuries with which the old obstetricians had to cope. We are no longer dealing with those injuries which sometimes appeared a week or two after delivery in the wake of the slough of pressure necrosis.

A low-residue diet was prescribed in half of the cases, frequently along with opiates. One physician even had his patient on liquids for two days. Enemas were withheld in 17 cases, while oil retention enemas were given 9 times, usually on the fourth or fifth day. Such management is contrary to the accepted postoperative care following rectal surgery today. The proctologists prefer their patients to have a normal stool early to dilate the anus and break down any folds and adhesions which might be forming in the rectum. Fecal impaction is also thereby avoided.[7] All the patients had adequate sphincter control when they were discharged from the hospital. Questionnaires were sent to the attending physicians to inquire into the fate of the thirty-seven patients following their discharge. These questionnaires were all answered and conveyed the following information:

At their examination six weeks post partum, these patients reported no anal sphincter difficulties. None showed any structural sequelae. There were no rectovaginal fistulas. One patient had some tenderness in the anal area which disappeared subsequently (Table V).

TABLE V. COMPLICATIONS AT FOLLOW-UP SIX WEEKS POST PARTUM

	PRESENT	ABSENT
Febrile morbidity	0	37
Tenderness in area of rectum	1	36
Impaired anal control	0	37
Rectovaginal fistulas	0	37

Seven of the 37 patients had one subsequent delivery in this hospital while one was delivered twice following her laceration. With these subsequent deliveries, median and mediolateral episiotomies were each used five times. The deliveries were all uneventful with one exception. In this last case, the patient's mediolateral episiotomy extended again into a third-degree laceration (Table VI).

TABLE VI. SUBSEQUENT DELIVERIES

NO. OF SUBSEQUENT DELIVERIES	NO. OF CASES	EPISIOTOMY USED	
		MEDIAN	MEDIOLATERAL
One	7	5	2*
Two	1	0	2

*Third-degree laceration again incurred in one case.

Comment

During the past three years, there has been a tendency in this hospital toward the use of the median episiotomy (Table VII). The popularity of the mediolateral episiotomy has accordingly somewhat suffered.

TABLE VII. YEARLY INCIDENCE OF THIRD-DEGREE LACERATIONS

YEAR	TOTAL DELIVERIES	THIRD-DEGREE LACERATION		MEDIAN EPISIOTOMY	THIRD-DEGREE LACERATION	MEDIOLAT. EPISIOTOMY	THIRD-DEGREE LACERATION	MEDIAN EPISIOTOMY IN PRIMIPARAS
		NO.	PER CENT					
1949	4,233	5	0.11	789	2	2,641	3	—
1950	4,292	4	0.09	843	3	2,752	1	139
1951	4,493	7	0.15	1,244	6	2,488	1	326
1952	4,837	8	0.16	1,422	4	2,599	4	231
1953	5,393	13	0.24	1,799	11	2,235	2	238
5 Year Period	23,248	37	0.15	6,097	26	12,715	11	

Median episiotomies lead to easier and more anatomical repairs; they bleed less and are much less painful during the postpartum period. Most obstetricians today are cognizant of those advantages of the median episiotomy and use it whenever they think that it will give them room enough to perform the delivery without incurring a third-degree laceration. Various criteria have been offered to facilitate making that decision, yet they are not foolproof.[8] It is always puzzling to the medical students and interns to see the staff doctors make up their minds on the type of episiotomy to be used in a given case. That no obstetrician is infallible in his evaluation of the stretching possibilities of a perineum is shown in our survey.

The favor into which median episiotomy has recently come has led to the practice of using it more frequently in delivering primiparas (Table VII). There is, however, no agreement as to how far one should go in this respect. The ratio of median to mediolateral episiotomies in primiparas of 5 obstetricians, all on the teaching staff of the University of Oregon Medical School, was as follows, respectively: 1:9, 1:3, 1:2, 1:1, and 6:1. None of these reported a third-degree laceration.

Some, impressed by the advantages of the median episiotomy, have adopted its routine use in all cases. They advise cutting through the anal sphincter and rectum when there is undue stretching of the perineum. They have found that the "complete perineotomies" thus performed heal well and cause no inconvenience or disability to the patient.[9]

We believe that there are certainly cases when a mediolateral episiotomy is the wisest choice. In our experience, the use of a median episiotomy with a tight perineum requires control of the extension of the head with forceps to let the tissues in the lower third of the vagina and around the introitus slide back from the head instead of being pulled by it. A certain amount of resistance is encountered in this process and unless one is a "complete perineotomy" enthusiast, it might be well to resort to a mediolateral episiotomy in certain cases—if the baby is small and premature, for instance, to avoid cranial damage.[10]

Another instance where a mediolateral episiotomy should be used is in the case where prompt and hurried repair of the episiotomy is desirable, and a third-degree extension appears a likely possibility. This may be the case, for example, in a multipara delivered under pudendal block for whom general anesthesia is contraindicated. Frequently, the relaxation of the perineum of

Fig. 1.

Fig. 2.

Fig. 3.

Fig. 1.—Two rows of submucosal stitches are used to close the rectal mucosa, everting the edges into the rectum.

Fig. 2.—The torn ends of the external sphincter are reapproximated with interrupted sutures in the fascial sheath. No sutures are placed through the muscle.

Fig. 3.—The episiotomy repair is completed in the usual manner.

such a patient will not be adequate for a good repair. The feeling of pain in the rectovaginal area may return rapidly, thus complicating further the task of the operator.

We agree with Dallas[11] that a mediolateral episiotomy is advisable with face and brow presentations, or when the infant is delivered as an occiput posterior. In general, it proves useful in deliveries where manual maneuvers are necessary. One would, for instance, prefer to have an intact posterior vaginal wall when a hand has to be introduced into the hollow of the sacrum to sweep out the baby's arm in a difficult breech delivery.

It should be remembered that the size of the skin incision in the perineum is not an accurate index of the amount of room available to the presenting part to slide out. We have often been surprised to see a primigravida with a small perineal body deliver a normal-sized infant without any extension of a relatively small episiotomy. In this connection, we believe that a very important part of the episiotomy consists in prolonging it inside the vaginal floor as far as necessary. The vaginal canal is surrounded by a musculofibrous sheath which, especially in primiparas, is often quite snug around the presenting part and impedes descent and extension. D'Errico's[12] advice in this regard is worth observing if lacerations are to be avoided. He prefers "multiple snips of the scissors" to the time-honored "single slash." It is evident that the single-slash technique, in the case of a median episiotomy, would cut through sphincter and rectum every time if it were made long enough to involve the vaginal floor. With mediolateral episiotomies, the failure to incise through the vaginal sheath will result in extensions of the episiotomy along the vaginal sulcus with the forceps blades.

One case in the series was thought worthy of special attention. According to the attending physician, the laceration was not truly of the third-degree type, as the external anal sphincter and rectal mucosa were not completely torn, although the rectovaginal wall had been lacerated above them. The lesion, however, was converted into a third-degree extension to facilitate repair. This rare type of injury was reviewed by Bret and co-workers in 1951.[13] They added 4 cases of their own to the 9 that they found described in the literature. They concluded their study by advising in those cases to do—as was done above—a perineotomy to convert the tear into a true-third degree laceration. Thus, they felt that the repair was more adequate and that the fistulas and incontinence could be avoided which were the common sequelae when nothing was done in the past or when the defect in the rectovaginal wall was simply obliterated with sutures.

In concluding, we must acknowledge the fact that median episiotomies are used more and more frequently in this hospital (they have more than doubled in the past five years), with a negligible (one per thousand) over-all increase in third-degree lacerations. This, coupled with the excellent results obtained following repair of the third-degree lacerations, makes one wonder whether, in the type of obstetrics that we practice today, the possibility of that complication is really a justifiable contraindication to median episiotomies. We note with interest that, in the last edition of his textbook, Eastman states that "a median episiotomy is a satisfactory procedure in nine out of ten deliveries."[14]

Management of the Third-Degree Laceration

Every physician who practices obstetrics today should be familiar with the anatomy of the perineum as it is exposed when a third-degree laceration occurs, for, no matter how careful he is and even if he is in the habit of doing mediolateral episiotomies exclusively, he may well sooner or later be con-

fronted with that complication. Such knowledge will also enable him to identify and repair properly partial lacerations or fascial tears affecting the anal sphincter which he might otherwise not recognize.

The first and most important step in the management of a third-degree laceration is an immediate, adequate repair. The most common technique of repair followed at Emanuel Hospital consists of a submucosal row of chromic No. 00 or 000 catgut interrupted sutures. The mucosal edges are thus everted into the lumen of the rectum. A second row of interrupted sutures is then placed over the first one. Care is taken not to puncture through the rectal mucosa during this procedure (Fig. 1) .

The torn ends of the external sphincter are then identified and the thick fascial layer around this sphincter reapproximated with chromic No. 00 catgut interrupted sutures, beginning posteriorly and working anteriorly. No sutures are placed through the muscle (Fig. 2).

The rest of the episiotomy is closed in the usual manner, reapproximating the structures anatomically rather than constricting them with tight sutures. It is best to avoid putting stitches in the outer aspect of the anal area as they are painful and local infection frequently ensues due to poor drainage (Fig. 3).

Another method which has been advised by some[15] was used twice in the series. It consists of closing the rent in the rectal mucosa with interrupted sutures which are tied inside the rectum. The protagonists of this technique thus avoid burying catgut under the rectal mucosa. We see two disadvantages to the method, however. First, it forces the operator to work inside the grossly contaminated rectum. Second, a number of puncture holes through the rectal mucosa are made by the needle which may later become the site of foci of infection with poor drainage.

The postpartum care usually need not be much different from that given in routine cases. The patient should not receive opiates after the day of surgery. She should be put on an anticonstipation diet (cooked fruits, cooked vegetables, salads, etc.). Bulk laxatives may be used beginning on the first postpartum day. Witch hazel packs may be used with advantage over the anal area, especially if hemorrhoids are present. An enema on the fourth postpartum day may be given if needed but will usually not be necessary with the management just described.

Summary

1. Thirty-seven third-degree perineal lacerations which occurred at Emanuel Hospital in the past five years are reviewed.

2. The incidence of these lacerations was 0.42 per cent with median episiotomies and 0.08 per cent with mediolateral episiotomies. They were frequently encountered in elective low forceps deliveries with patients of low parity.

3. No anal sphincter difficulties or rectal complications were found in this series. There was no febrile morbidity.

4. Subsequent deliveries were not accompanied by dystocia.

5. Median and mediolateral episiotomies are discussed in relation to the danger of third-degree lacerations.

6. A technique for repair and postpartum care is outlined.

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FETAL SURVIVAL IN 376 TWIN DELIVERIES*

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DESPITE the great advances in the improvement of fetal and maternal mortality, twin pregnancies and deliveries still present formidable hazards to both mother and children. The great importance of prematurity as the cause of the high fetal mortality in twin deliveries has been stressed by many investigators. The increased incidence of toxemia of pregnancy, polyhydramnios, uterine inertia, and postpartum hemorrhage in twin pregnancies and deliveries is now common knowledge.

The objective of this survey and analysis undertaken at the Beth-El Hospital was to find possible aspects in the management of labor and delivery of twins which could be altered with the possibility of effecting some improvement in their survival rate.

Material and Incidence

This study covers the period of 1940 to 1952, during which time a total of 41,872 patients were delivered at the hospital. Of this number, 375 patients delivered twins and one patient delivered triplets. The triplets are included in this study because whatever factors there may be in the management which influence the outcome of twin pregnancy and delivery apply equally well to triplets. No attempt is made to compare the deliveries accomplished in service cases delivered by residents and interns to those managed by members of the obstetrical department.

In considering fetal analysis, statistics, and survival, we must bear in mind that we consider a twin pregnancy as two fetuses; that the fetuses may or may not survive together or separately, and therefore, base our studies and statistics on each of the twins separately, referring to the first of the twins as baby A, and to the second one as baby B.

The over-all incidence including the triplets is 1 in 111.4 deliveries. We must explain, however, that pregnancies under 18 weeks' duration are not admitted to our obstetric department. Those early pregnancies with twins are not included in this study. Their inclusion would make a difference in the incidence. Potter and Crunden[9] report an incidence of 1 in 91 patients delivered at the Chicago Lying-in Hospital and 1 in 106.6 inpatients delivered at home, with an over-all incidence of 1 in 93.4. Munnell and Taylor[8] report an incidence of 1 in 113 at the Bellevue Hospital. Strandskov,[10] in a study of 28 million births in the United States, found the incidence to be 1 in 88.6 for the white and 1 in 70.69 for the Negro population. Guttmacher[3] reported that, in 57 million births in the United States, the incidence of viable twin births was 1 in 92.4 deliveries among the white population, while in the Negro it was 1 in 73.8.

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Age and Parity

We divided the patients into four groups, with six-year age differences, to find the ages at which time the incidence of twins is greatest. Of the 376 multiple pregnancies, 73, or 19 per cent of the mothers were between the ages of 18 and 23; 160, or 43 per cent, between 24 and 29; 115, or 31 per cent, between the ages of 30 and 35 years. Table I shows the greatest number of twins to occur between the ages of 18 and 35 years, during which ages 93 per cent of the twin pregnancies occurred; the majority of these, 62 per cent, occurred before 30 years of age.

TABLE I. OCCURRENCE OF TWINS AT VARIOUS AGE GROUPS

AGE	NO. OF PATIENTS	PER CENT
18-23	73	19
24-29	160	43
30-35	115*	31
36-42	28	7
Total	376	100

*Includes one triplet.

The incidence of twin pregnancies in the more youthful patients seems to run parallel with the parity as shown in Table II. Twin pregnancy occurred most frequently in the primigravidas, with the second gestation running a close second. The 158 patients in the primigravid group constituted 42 per cent of the total series, and 145 patients pregnant for the second time 38.6 per cent. The combined total of patients with first or second pregnancies was 80.6 per cent of the women who delivered twins, and only 19.4 per cent of all the rest of greater multiparity, a ratio of almost 4 to 1.

TABLE II. PARITY AND THE OCCURRENCE OF TWINS

PARITY	NO. OF PATIENTS	PER CENT
0	158	42
i	145	38.6
ii	56	15
iii	9	
iv	4	
v	2	4.4
vi	1	
vii	0	
viii	1	

Potter and Crunden[9] found in their series that 29.6 per cent of the twin pregnancies were in primigravidas, and 25.3 per cent were in second pregnancies, the combined total being 54.9 per cent.

Duration of Pregnancy

The duration of pregnancy is an important factor in multiple pregnancy because of the prematurity resulting from early labor. Were it possible to stave off labor for one month in the earlier gestations, the hazard of prematurity could be overcome and the fetal survival rate would show a striking improvement. Table III summarizes the duration of pregnancy in weeks, of the four groups into which we divided the total number of twin pregnancies of 18 weeks or over. We found 102 patients, or 27.1 per cent, with gestations up to and including 35 weeks. Pregnancies of 36 weeks and over constitute 72.9 per cent in our analysis. Munnell and Taylor[8] found 53 per cent in a similar grouping. McIlroy and Evans[7] found that 64 per cent of the twin pregnancies in their series went to term, 24 per cent were premature, and 8 per cent

aborted. They do not state their criteria for "term" and "premature." Potter and Crunden[9] found the average duration in twin pregnancy to be 256 days. Guttmacher[2] in a carefully controlled group found that the twin pregnancies usually terminated more than two and one-half weeks earlier than single pregnancies, and that 257.8 days was the average duration of pregnancy in term and premature twin pregnancies. On the basis of these studies 37 weeks was considered the average duration of pregnancy in twins. In our series, 37 weeks was the average duration for the entire group of mature and premature twin pregnancies.

TABLE III. DURATION OF PREGNANCY

WEEKS OF GESTATION*	NO. OF PATIENTS	PER CENT
18-27	12	3.2
28-35	90	23.9
36-40	259	68.9
Over 40	15	4.0
Total	376	100.0

*Patients with gestations under 18 weeks are not admitted to the Obstetric Department.

Anesthesia and Analgesia

Perhaps in the field of hypnotics, analgesics, and anesthetics something can be done to alter the survival rate of twins, though scant mention is made of the subject in previous studies on twin delivery. A perusal of the current textbooks on obstetrics and the current literature discloses a rather insufficient discussion as to which analgesic or anesthetic is best suited for labor in the delivery of twins. Hirst[5] tabulated 254,000 births of over 20 weeks' gestation and found four times as many stillbirths in twin pregnancies and five times as many neonatal deaths as in single births. Munnell and Taylor[8] tabulated the results of a ten-year study of twins at the Bellevue Hospital and found that the gross fetal mortality rate was four times that for single pregnancies. They found prematurity to be the greatest cause of death in twin deliveries. Prematurity is conceded by all writers on the subject to be the greatest hazard to twins, and their respiratory apparatus to be the most vulnerable.

It is known that narcotic and amnesic agents, and all forms of inhalation anesthesia are respiratory depressants. Choice of the type of analgesia or anesthesia to be used in such deliveries poses, therefore, an important problem if we are to avoid anoxia, atelectasis, pneumonitis, etc. Greenhill[4] states that for the actual delivery the safest anesthesia for the infant is direct local infiltration, caudal, or saddle block analgesia. Lull and Hingson[6] are of the opinion that, if continuous caudal analgesia is used, a general anesthetic should be superimposed if a podalic version is to be performed on the second of twins, and that, generally, regional block is not suitable for the delivery of the second of twins.

In a brief discussion as to the best anesthetic for the delivery of twins, Eastman[11] states that gas-oxygen is the most frequently used anesthetic. He found several disadvantages in its use, however. First, the fetuses are usually small, and inhalation anesthesia always presents a risk for small infants. Second, if ether is given it promotes relaxation of the uterus, with the increased possibility of postpartum hemorrhage.

The anesthetic or analgesic of choice would necessarily be one which would not be a cardiac or respiratory depressant, and would hinder least the natural progressive processes of labor, and be reasonably safe for the mother and baby.

With that in mind, we found conduction analgesia to have given us the most suitable adjunct for the delivery of multiple pregnancies.

In 1943 continuous caudal analgesia was added to our other forms of anesthesia—general, local, and fractional spinal, and five years later saddle block was added. The use of all these various forms of analgesia and anesthesia afforded us an opportunity for making comparative studies between conduction and other forms of anesthetics for the delivery of twins.

Table IV shows the various analgesics and anesthetics used in this series under study and Table V indicates not only the number of patients who received a certain type of anesthesia or analgesia but also at what gestational period. This is done to show the equal conditions in the distribution of conduction and inhalation anesthesias from which our conclusions are drawn.

TABLE IV. ANESTHESIA AND ANALGESIA

Continuous caudal	126
Saddle block	52
Fractional spinal	7
Nitrous oxide oxygen	67
Nitrous oxide ether	47
Nitrous oxide local	31
Ether	4
Local infiltration	14
No anesthesia	28
Total	376

Omitting the 14 cases where local infiltration was used, 185 patients were delivered under some form of conduction analgesia and 149 under some combination of inhalation anesthesia. Ten of this series were delivered by cesarean section, 7 of them with fractional spinal and three with continuous caudal analgesia. Twenty-eight patients delivered without any form of anesthesia (Table V).

TABLE V. ADMINISTRATION OF ANESTHETIC AGENTS AT VARIOUS GESTATIONAL PERIODS

ANESTHETIC	UNDER 28 WKS.	28-35 WKS.	36-40 WKS.	OVER 40 WKS.	TOTAL
Conduction	1	40	132	5	178
Fractional spinal	0	2	5	0	7
Inhalation	3	35	106	5	149
Local	0	4	10	0	14
None	8	9	6	5	28
Total	12	90	259	15	376

Duration of Labor

We consider the duration of labor an important factor in fetal survival, especially in prematurity and in the presence of ruptured membranes.

The shortest duration of labor, barring a precipitate one, with the least traumatic delivery seems, therefore, to be best suited for the delivery of twins. Munnell and Taylor[8] found that multiple pregnancy had no appreciable effect on the duration of labor in primiparas or multiparas, first stage or second stage.

Because of their terminal use, inhalation and local anesthesia have no effect upon the duration of the first or second stage of labor. Conduction analgesia, however, because it is instituted during the first stage or in the beginning of the second, does shorten labor. The longest duration of labor for baby A was 34 hours under conduction analgesia, and 53 hours under

general, local, or no anesthesia. The average duration of the combined first and second stages for baby A was 7 hours with conduction analgesia, and 10.3 hours with the other forms of anesthesia. The longest duration for the delivery of baby B was 30 minutes under conduction, and an hour and 25 minutes for inhalation anesthesia, and 53 minutes where local or no anesthesia were used. Inhalation anesthesia undoubtedly delays the birth of baby B many times unless version and extraction are performed without much delay.

With few exceptions the second stage for the second of twins was short. This is due to our advocacy of podalic version and extraction for the second of twins, unless it presents by the breech, or the head engages promptly and forceps may be applied, or delivery of the B baby proceeds rapidly. As soon as the first infant has been delivered and removed to the bassinet, steps are immediately taken to effect the delivery of the second twin.

The duration of the third stage after delivery of twins seems to run parallel with the duration after delivery of single births; that is, it is longest when general anesthesia was administered or none given. Table VI gives the longest, shortest, and average lapse of time between the delivery of the B baby and the delivery of the placenta.

TABLE VI. LENGTH OF THIRD STAGE

ANESTHESIA	THIRD STAGE		
	SHORTEST (MINUTES)	LONGEST (MINUTES)	AVERAGE (MINUTES)
Conduction	1	28	7.0
Inhalation	1	105	12.9
Local or none	2	80	15.5

The longest duration of the placental stage was 28 minutes under conduction with 7 minutes as the average; while in inhalation anesthesia it was one hour and 45 minutes as the longest time, and about 13 minutes as the average. With local or no anesthesia the longest third stage was 80 minutes, with 15½ minutes as the average.

Method of Delivery

Our method of delivery of the first twin did not vary much from that of single births. Those presenting by the vertex were delivered in the usual manner, except that we favor the application of low forceps to shorten the second stage rather than to permit a longer second stage with a spontaneous delivery. This is particularly applicable with conduction analgesia where the perineum is well relaxed but the absence of bearing-down pains delays spontaneous delivery. The avoidance of prolonged pressure of the fetal head on a rigid perineum, particularly in prematures, is believed to minimize the incidence of intracranial hemorrhage. Decomposition of a breech, breech extraction, and version and breech extraction are accomplished with ease, the procedures being performed in the interval between uterine contractions. These maneuvers are also facilitated by the preparation of the vagina and cervical canal by the delivery of the first twin. Only on rare occasions has it been necessary to supplement with general anesthesia, not so much to facilitate the version as for the patient's comfort. It might well be that in such rare cases the level of anesthesia was not high enough or was incomplete. It may also be likely that the necessity for total uterine relaxation, as accomplished by inhalation anesthesia, is not as necessary for the accomplishment of version and breech extraction as we believed it to be. Despite the preponderance of small babies, episiotomy was the usual procedure.

As we stated before, we advocate the performance of podalic version and breech extraction on the second twin unless it is in cephalic presentation and

the delivery proceeds rapidly. Munnell and Taylor state that, after a wait of twenty minutes after the delivery of the first twin, 63 per cent of the second twins in their series had to be delivered by operative procedures. As our experience has been similar, our procedure has been that as soon as the first infant is delivered and removed to its heated crib in the delivery room, steps are taken immediately to effect the delivery of the second twin. We have no established minimal or maximal waiting period. If version and breech extraction or the decomposition of a breech is to be performed, such procedure is best done immediately after the delivery of the first baby while the passages are still dilated and the amniotic fluid of the second sac not yet drained off.

Spontaneous deliveries occurred 207 times for both "A" and "B" babies, 276 were delivered by forceps, 170 were breech deliveries, and for 80 of the second twins version and breech extraction were performed, 20 times under inhalation and 60 times under conduction anesthesia (Table VII).

TABLE VII. METHOD OF DELIVERY*

	CONDUCTION		INHALATION†		LOCAL OR NONE		TOTAL
	A	B	A	B	A	B	
Spontaneous	15	7	74	56	27	28	207
Forceps	130	60	46	26	8	6	276
Breech extraction	30	48	30	47	7	8	170
Version and breech extraction		60		20			80
Total	175	175	150	149†	42	42	733

*Ten cesarean sections, 3 under caudal and 7 under fractional spinal not included in the figures.

†Includes one triplet.

There were 10 cesarean sections in this study, 7 of them under fractional spinal and 3 under continuous caudal analgesia. The indications were previous section 5, cephalopelvic disproportion 2, transverse lie 1, toxemia and ineffectual labor 1, prolapsed cord and brow presentation, 1.

Sex

In our series the usually quoted ratio of females to males in all births was reversed (Table VIII). Of the first twin there were 179 males to 196 females; of the second twin there were 182 males and 195 females. In one infant the sex could not be determined.

TABLE VIII. SEX OF INFANTS

	A	B	TOTAL
Male	179	182	361
Female	196	195	391
Undetermined		1	
Total	375	378	753

Weight

We mentioned previously the words "premature" and "term," as used by other writers. It is now time for us to define them specifically and state our standards. Some authors have chosen the word "term" to indicate a certain attained weight, and "premature" for those infants that did not reach it. We prefer to use the words "mature" and "premature" to denote these standards. Weight has been adopted by most authors to be the criterion for mature and premature infants. Other authors think that the length of the fetus is a more accurate indication of maturity. We agree with Guttmacher[2] that in the hands of inexperienced personnel the errors involved are too great;

and while we have the length of each baby listed along with the weight, we have disregarded it in the final estimate of the maturity of the baby and adopted weight as the sole criterion. The standards we use are 2,500 grams and over as being mature and under 2,500 grams but not less than 1,000 grams as being premature. In all of our calculation, we considered each twin pregnancy as two fetuses and placed each fetus in the weight category where it belonged in estimating the number of mature and premature infants, and in estimating fetal survival. Those under 1,000 grams are listed, but as such fetuses are considered nonviable they are not included in the fetal survival statistics.

Of the 573 babies delivered, 291, 38.6 per cent, weighed 2,500 grams or over and are therefore called mature; 434 infants, 57.6 per cent, were premature, weighing under 2,500 grams, but over 1,000 grams; and 28 of the fetuses, 3.8 per cent, were under 1,000 grams and considered nonviable (Table IX).

TABLE IX. INCIDENCE OF MATURITY AND PREMATURITY

	NUMBER	PER CENT
Mature	291	38.6
Premature	434	57.6
Previable (under 1,000 grams)	28	3.8
	753	100.0

Potter and Crunden[9] found that in their series 43.6 per cent were premature and 5.2 per cent previable. Guttmacher[2] in his series found 49 per cent of the twin pregnancies were mature. He considered a pregnancy at term or mature if even one of the twins weighed 2,500 grams or over. In our series, as stated previously, we considered the weight of each baby separately. When one considers that in single births only about 9 per cent are premature, the tremendous increase in prematurity in twin pregnancies is at once apparent as the cause of the increased fetal mortality (Table IX).

The smallest weights we encountered were 510 grams for baby A and the same for baby B; the largest weights were 3,770 grams for A and 3,856 grams among the B babies. The second twins were slightly larger.

Table X shows the weights of the infants in relation to the type of anesthesia under which they were delivered; for, as is to be expected, the heavier babies are to be found in the group delivered under continuous caudal analgesia where precipitate or imminent deliveries are not likely to occur, and when there is enough time to institute the analgesic. Those delivered under saddle block and inhalation anesthesia are about equal in weights.

TABLE X. ANALGESIA IN RELATION TO BABY WEIGHT

	BABY "A" (GRAMS)	BABY "B" (GRAMS)
Caudal Analgesia.—		
Smallest	510	510
Largest	3,770	3,856
Average	2,580	2,608
Saddle Block.—		
Smallest	510	1,077
Largest	2,778	2,892
Average	2,070	2,155
Inhalation, Local, or None.—		
Smallest	510	623
Largest	3,260	3,289
Average	2,070	2,155

Fetal Complications

Prematurity is the leading cause of fetal death in the neonatal period. Of the 725 infants that weighed over 1,000 grams, 434, 57.6 per cent, were premature. Of this premature group, 64 infants died of all causes, resulting in a mortality rate of 14.7 per cent; while of the 291 mature babies only 7 died, a mortality of 2.4 per cent. The fetal loss in premature infants was, therefore, six times as great as that in mature ones. Next in frequency were the respiratory complications, followed in frequency by cerebral and visceral hemorrhages. Some form of erythroblastotic disease due to blood-group incompatibilities occurred 5 times, injuries occurring during delivery were encountered 5 times, there were 2 cases of facial palsy, one of Erb's palsy, one of fractured clavicle, and one case of separation of an epiphysis (Table XI). The fetal respiratory system is particularly vulnerable to respiratory depressants, among which is inhalation anesthesia; and, as is shown in Table XII the greatest number of respiratory complications occurred in the group delivered under inhalation anesthesia. In this group there were 10 infants with aspiration, 10 with atelectasis, 2 with narcotization, one with bronchopneumonia; while in a larger group delivered under conduction analgesia there were only 5 instances of atelectasis and 6 of aspiration, no narcotized babies, and no pneumonia. The situation was the same with cerebral hemorrhage; there were 4 in the inhalation group and only 2 in the conduction group.

TABLE XI. FETAL COMPLICATIONS IN 753 TWINS

Aspiration		17
Atelectasis		16
Intracranial hemorrhage		7
Visceral hemorrhage		8
Erythroblastosis		5
Macerated fetus		4
Injuries		4
Erb's palsy	1	
Facial palsy	2	
Fractured clavicle	1	
Separation epiphysis	1	
Narcotization		2
Malformations		3
Hydrocephalus		1
Parotid infection		1
Bronchopneumonia		1

TABLE XII. FETAL COMPLICATIONS IN RELATION TO ANESTHESIA

	CONDUCTION 370 INFANTS	INHALATION 299 INFANTS	LOCAL-NONE 84 INFANTS
Aspiration	6	10	1
Atelectasis	5	10	1
Bronchopneumonia	0	1	0
Narcotization	0	2	0
Cerebral hemorrhage	2	4	1
Total	13	27	3

A number of the listed complications and anomalies occurred simultaneously in the same fetus, so that the number of complications listed does not necessarily represent so many babies.

Maternal Complications

The most frequent maternal complication and the one that has a particular bearing upon the ultimate fetal outcome is toxemia of pregnancy. In

our series toxemia of pregnancy occurred 19 times, or in 5 per cent of the cases. This is a smaller incidence than reported by other investigators. Potter and Crunden,[9] for instance, report 62 cases of toxemia in their series of 332 multiple pregnancies, or 18.7 per cent.

Our toxemia group included 3 cases of eclampsia one of which occurred post partum. Next in frequency of maternal complications were the ante, intra, and postpartum hemorrhages. There were 15 instances of postpartum hemorrhage requiring transfusions. Ablatio placentae was found in 4 instances, retained placenta in 3, and placenta previa in 2 patients. Polyhydramnios was encountered once. There were no maternal deaths in this series (Table XIII).

TABLE XIII. MATERNAL COMPLICATIONS IN 376 TWIN DELIVERIES

Toxemia of pregnancy	19
Postpartum hemorrhage	15
Uterine inertia	4
Ablatio placentae	4
Placenta previa	2
Prolapsed cord	4
Retained placenta	2
Polyhydramnios	1
Separation of symphysis	1

Fetal Mortality and Fetal Survival

After the previous factual tabulations and statistics, we now return to our original thesis, the quest for possible avenues for improvement of the fetal survival rate. Since prematurity with all its implications is the greatest cause of fetal death, can anything be done to prolong the pregnancy? Bender[1] of Liverpool, in a review of 472 twin deliveries, says that the object of the antenatal care in twin pregnancy should be to prevent the premature onset of labor, and suggests that every woman with a twin pregnancy be hospitalized for bed rest after the thirty-third week, or sooner, if there are additional complications. In his series, bed rest was attended by a significantly lower immaturity rate. We have had no experience with this method. It is logically good, albeit economically and socially probably a difficult task in most cases.

TABLE XIV. FETAL OUTCOME

MATURE						PREMATURE					
LIVING		STILLBIRTH		NEONATAL DEATH		LIVING		STILLBIRTH		NEONATAL DEATH	
A	B	A	B	A	B	A	B	A	B	A	B
Conduction Analgesia (366 Infants).—											
79	71	0	0	0	1	96	100	2	4	6	7
		Fetal mortality in mature infants							0.7%		
		Fetal mortality in premature infants							8.8%		
		Total fetal mortality							5.4%		
Inhalation Analgesia (293 Infants).—											
61	60	1	2	1	1	66	64	3	6	15	13
		Fetal mortality in mature infants							4.0%		
		Fetal mortality in premature infants							22.2%		
		Total fetal mortality							14.0%		
Local or No Anesthesia (66 Infants).—											
8	5	1	0	0	0	20	24	1	1	3	3
		Fetal mortality in mature infants							7.1%		
		Fetal mortality in premature infants							15.4%		
		Total fetal mortality							13.6%		

The other phases where possible improvement may be effected are labor and the pediatric care of the infant. As the latter is a subject for pediatricians and not within the scope of this study, we will confine ourselves to the labor and the delivery, during which changes in the administration of pain-relieving measures and changes in the methods of delivery may be sufficient to alter the fetal outcome. As mentioned previously, the most vulnerable part of the premature infant is the respiratory system. Consequently, any agent which is a respiratory depressant that can pass the placental barrier when administered to the mother will affect the infant adversely. This is particularly true of narcotics, hypnotics, barbiturates, and volatile gases.

It is during delivery that a suitable anesthetic should be employed. One might reason that, to avoid the deleterious effects of the previously mentioned agents, no anesthesia or the application of local analgesia would be the answer. Our statistical evaluation shows the reverse to be true (Tables XIV, XV, and Fig. 1). The fetal mortality rate in the 66 infants delivered with local or no anesthesia was 7.1 per cent in the mature, and 15.4 per cent in the premature, with an over-all fetal mortality rate of 13.6 per cent. This rate is similar to those for delivery under inhalation anesthesia. In 293 infants there was a mortality rate of 4 per cent in the mature, and 22.2 per cent in the premature, and an over-all fetal mortality rate of 14 per cent. In contrast to these figures,

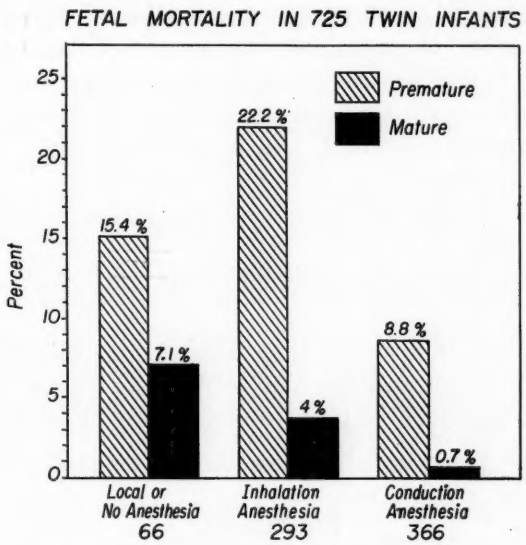

Fig. 1.

conduction analgesia for 366 infants showed a mortality rate of 0.7 per cent in the mature, and 8.8 per cent in the premature, with an over-all fetal loss of 5.4 per cent.

The additional value of conduction analgesia is that it can be instituted early enough in labor to avoid depressant agents, and yet have an efficient anesthetic effect for terminal delivery.

We found the mortality rates almost equal for the first and the second twins.

We may conclude that twinning in itself does not present any greater hazard for the first or second twins, and the mortality rate is not greater than in single births.

TABLE XV. TOTAL FETAL OUTCOME IN DELIVERY OF 753 TWINS*

ANESTHESIA OR ANALGESIA	LIVING		STILLBORN		NEONATAL DEATHS		FETAL LOSS (PER CENT)
	MATURE	PREMATURE	MATURE	PREMATURE	MATURE	PREMATURE	
Conduction analgesia	150	196	0	6	1	13	5.4
Inhalation anesthesia	121	130	3	9	2	28	14.0
Local or none	13	44	1	2	0	6	13.6
Total	284	370	4	17	3	47	9.8

*28 fetuses under 1,000 grams not included.

Summary and Conclusions

1. A series of 376 twin pregnancies and deliveries is reviewed as to incidence, age, parity, and duration of pregnancy.

2. The various anesthetics used in the conduct of labor and delivery of these twins are listed.

3. The methods of delivery of the first and second of the twins are described and statistically enumerated.

4. Maturity and prematurity are defined and criteria are established according to infant weight, with percentages of their incidence.

5. Fetal and maternal complications are listed and comparisons made with their incidence in similar studies of other investigators.

6. Fetal mortality rates and fetal survival are discussed.

7. Statistical studies are made and percentages given of fetal mortality rates with each form of anesthesia used for the delivery.

8. Our methods of delivery are discussed, particularly as to the increase of operative procedures.

9. The increase of operative procedures did not affect adversely the fetal survival rate.

10. The conclusion is reached that conduction analgesia may safely be administered during labor and for the delivery of twins, and that it favors the increase of fetal survival despite the increase of operative procedures.

We wish to express our appreciation to members of the staff for permission to include their cases in this study.

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1333 PRESIDENT STREET

VULVAR TUBERCULOSIS IN PREGNANCY

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ALTHOUGH first described in 1771 by Morgagni, vulvar tuberculosis is still a very rare entity. Primary vulvar tuberculosis is even a greater rarity and when associated with pregnancy is indeed very rare. It has two basic types, ulcerative and hypertrophic, both of which, however, may be present in the same patient.

After presenting a brief review of the literature, we have abstracted three cases of vulvar tuberculosis in pregnancy in two of which ulcerative lesions predominated and in one of which the lesions were hypertrophic. To these we have added a more detailed account of our own case which was of the primary hypertrophic type.

Review of the Literature

Norris[26] reported combined statistics of 379 cases of genital tuberculosis with no vulvar involvement. In 571 postmortems on tuberculous females, Auerbach[1] found 9.1 per cent of tuberculosis of the genital organs, but no vulvar case recorded. Bulkley[7] presented his case and mentioned 71 cases of vulvar tuberculosis which occurred between 1771 and 1915. Since 1915, several cases have been added to the literature. Most cases appear to be of the secondary type with a past or present history of tuberculosis of the lungs or elsewhere.[6, 8, 11, 22, 23, 24, 31, 37] In Quinet's[30] case the cervix was affected before the vulvar lesion appeared. Cases are reported which occurred as a result of the first coitus,[10, 13, 15, 22, 29, 31, 32, 33] the majority having had mates suffering from genitourinary tuberculosis[10, 15, 20, 29, 31, 34] and active pulmonary tuberculosis.[2, 15, 16] A few cases are reported by Popoff,[29] Natale,[23] and Plassat[28] without a history of previous coitus but with past histories of pleurisy or neck and supraclavicular adenopathy.

Although the majority of the cases were of the secondary type, the literature presents also a small number of primary cases.[4, 16, 19, 21, 32, 34]

Women in the years of active sex life were most affected. The great majority had had sex experience. The nulliparas were just as much affected as the multiparas, but it is not possible to record the parity in relation to the exact time of appearance of the disease. It was found only occasionally in children and in menopausal women.[23, 40]

Cases are reported in children who had contact with tuberculous parents or attendants. As with tuberculous males contamination occurs through the sputum,[25, 29, 36, 38] or by contact with clothing or surroundings, or by masturbation.

The mortality rate was considerably higher in the secondary type of cases. Death usually occurred from tuberculosis, chiefly miliary.[3, 5, 18, 24, 30, 35, 40]

Lesions

Although vulvar tuberculosis can be seen in its hypertrophic chronic growth, as a rule the disease presents itself with an ulcerative lesion resembling chancre or chancroid. Commonly associated with swelling of the inguinal nodes, frequently other adenopathies, though less common, may be present. Fistulous lesions may become chronic, showing seropurulent exudate.[28, 29] The hypertrophic type represents the chronic state with frequently painless growth formation, unilateral or bilateral, with or without any apparent ulcer.[27] Masses may develop to enormous size.[6, 12] In Fernandes'[12] case, the patient was unable to walk because of the large tumors. Taussig[39] believed the hypertrophic lesion to result from obliterative endarteritis and blocking of lymph channels.

Diagnosis

Differential diagnosis is of major importance. Granuloma and lymphogranuloma inguinale, chancre, chancroid, carcinoma, and gumma should be considered. Serological tests, Ducrey, Frei skin tests, dark-field examinations, biopsies, smears and cultures of the suppuration from the lesion or the lymph node for acid-fast bacilli may be indicated for differential diagnosis. Animal inoculation is needed to differentiate the two acid-fast bacilli, Koch and smegmatis.

CASE 1.—(Ulcerative type.) Gaté and associates[14] report a case of an 18-year-old woman, two months pregnant, who had vulvar ulceration and edema, together with palpable inguinal lymph nodes and erythema nodosum on both thighs. The chest was negative for tuberculosis. Her husband was healthy. The ulcer was cauterized, the nodes were aspirated, and Koch bacilli found. Guinea pig inoculation was positive for tuberculosis. Cauterization cured the ulceration. Gonnet and collaborators,[18] reporting later on the same case, stated that her prenatal course was uneventful. At eight months she went into labor. The previous ulcer had healed. A small, fistulous tract persisted at the site of the purulent adenitis. Labor and delivery were easy. The baby weighed 5 pounds and was in good condition. The patient became febrile in the twenty-four hours after delivery, however, and died of miliary tuberculosis sixteen days later.

CASE 2.—(Ulcerative type.) Gibson[17] presents a case of vulvar tuberculosis in a woman who was four months pregnant when she noted a small ulcer. She had been married for eight months, had arrested pulmonary tuberculosis four years prior to her pregnancy and healed tuberculous lesions of the second, third, and fourth lumbar vertebrae. The pregnancy was allowed to go to term. The lesion on the vulva healed. Intravenous pyelogram showed no secretion from the right kidney. Delivery was by forceps. The puerperium was normal. Twenty days post partum, after ten daily urine specimens were found positive for tuberculosis, nephrectomy and ureterectomy were done for a tuberculous pyonephrosis. She recovered. Six months later she became pregnant and the pregnancy was terminated by dilatation and curettage.

CASE 3.—(Hypertrophic type.) Petit and Bender[27] reported a case similar to ours, which follows. Their patient was a 31-year-old gravida iii, para ii, two months post partum. During her first gestation, she noticed a uniform increase in the size of the

vulva. During her third pregnancy, vegetations and growths appeared in addition to the hypertrophy. No ulceration was present, no pain. The pelvis was negative. The chest was negative. No history about the husband was obtained. Surgery with excision of the masses was done followed by healing by first intention without ulceration. Histological and bacteriological examinations revealed tuberculosis. Her last pregnancy terminated with a forceps delivery.

Case Report (Hypertrophic Type)

K. B., a 31-year-old para iii, gravida iii, was admitted to the Obstetrical Service of the Harlem Hospital on May 12, 1953, for evaluation of the type of delivery because of a previous operation on the vulva. The last menstrual period was Aug. 15, 1952, and the expected date of confinement was May 22, 1953. She had attended the prenatal clinic uneventfully since April 1, 1953. She was discharged on May 21, 1953, and readmitted in labor on May 22, 1953.

The patient had had a removal of bilateral vulvar masses on Feb. 24, 1953, during the sixth month of this pregnancy. These were found to be of a tuberculous nature.

Family History.—Tuberculosis, cancer, and syphilis were denied. The husband, who was reported to be healthy, had been discharged from the Army about the time the patient first noted the swelling of the right labium. He never had to have urological treatment as far as she knew.

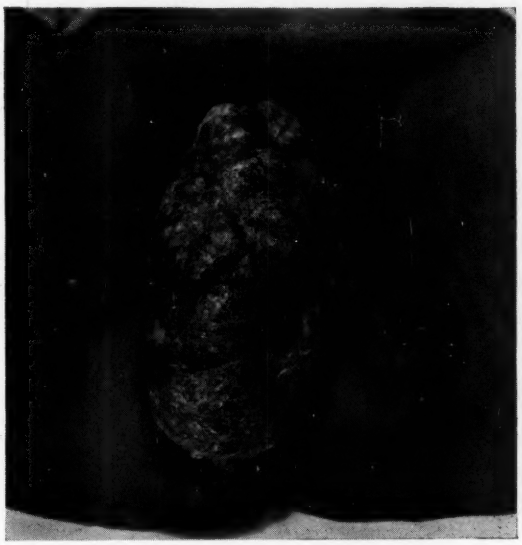

Fig. 1.—Preoperative appearance of the vulva.

Obstetrical History.—She was gravida iii, para ii. Her first delivery, in 1948, was spontaneous, her second, in 1950, by forceps. The first baby, that weighed 5 pounds, 6 ounces, at birth, died ten days post partum of "hemorrhage of the brain." The second baby weighed 6 pounds, 13 ounces, at birth, and was alive and well.

Gynecological History.—There was no history of dysmenorrhea or pelvic inflammatory disease. Her menstrual periods had begun at the age of 13, and occurred every twenty-five days, lasting four days.

The patient had noticed a small swelling in the right labium in 1949, at which time she was two months pregnant. She was treated at the Skin Clinic of the Harlem Hospital with liver extract and vitamins. After delivery, in October, 1950, a biopsy was done, tuberculosis was discovered, and she was treated with streptomycin. The "swelling"

grew to become an irregular growth about the size of an egg. Following delivery in 1950, the patient noted other "swellings" in the left labium, the inguinal regions, and the inner parts of both thighs. These swellings broke down and discharged pus. They eventually healed, forming scars. The mass of the right labium started growing again at the onset of the present pregnancy and developed to the size of a large orange, irregular in shape and firm. She was unable to walk comfortably and had moderate pain. She was hospitalized on the Gynecological Service for more definitive treatment. There was no evidence of tuberculosis elsewhere (Fig. 1).

During the time she was on the Gynecological Service, she was treated with 1 Gm. of streptomycin daily, together with 600,000 units of penicillin, Rimifon,* 100 mg. daily, blood transfusions, and supportive therapy with iron, liver extract, and vitamins.

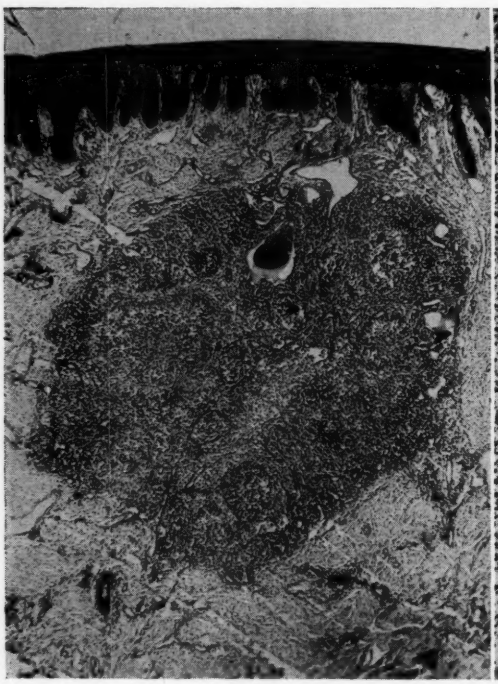

Fig. 2.

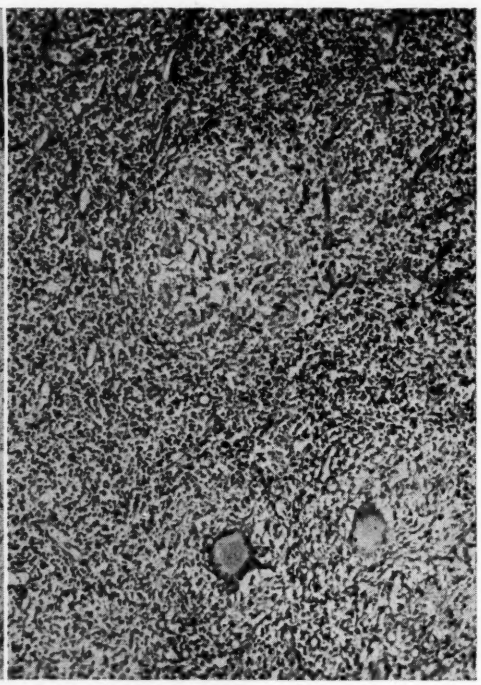

Fig. 3.

Fig. 2.—Right labium: a conglomerate tubercle in the deep corium. Lymphatic stasis in the surrounding tissue. (Low power. Hematoxylin-eosin stain.)

Fig. 3.—Right labium: high-power magnification of Fig. 2. (Hematoxylin-eosin stain.)

The sedimentation rate varied from 20 mm. in 30 minutes to 7 mm. in 30 minutes. There was a moderately severe secondary anemia with hypochromia. The white count before operation showed a moderate leukocytosis with a normal count after operation.

Blood chemistry tests were normal. Urinalysis was negative. Tuberculin tests were negative. Serological tests were negative. Frei tests were negative. X-ray of the chest was normal. A biopsy on Feb. 3, 1953, revealed nonspecific granulomatous lesions of the skin with marked lymphectasia. Deeper biopsy was thought desirable.

A right vulvectomy, together with excision of smaller masses on the perineum and left labium, was performed on Feb. 24, 1953. The largest lesion measured 16 by 8.5 by 4.5 cm. Varidase† was used postoperatively.

*Rimifon (isonicotinylhydrazine) manufactured by Hoffmann-LaRoche, Inc., Roche Park, N. J.

†Varidase (streptokinase-streptodornase) manufactured by Lederle Laboratories, Pearl River, N. Y.

The pathological report after operation showed portions of tuberculous granulation tissue with lymphatic stasis on the periphery (Figs. 2, 3, and 4). A smear from the granulation tissue was negative for acid-fast organisms. Culture was positive for acid-fast organisms. Guinea pig inoculation was then done to exclude the possibility of contamination of the material by the smegma bacillus (also acid fast) which, however, is not pathogenic for guinea pigs. Autopsy of the guinea pig confirmed the diagnosis of tuberculosis.

The postoperative course was uneventful and healing was good.

Delivery.—On her admission to the Obstetrical Service, the blood pressure was 100/60, temperature 98° F., pulse 74. No nodes or collateral circulation were observed in the neck. The heart was normal; the lungs were clear. On the skin several scars from previous lesions were present in the inguinal regions and on the inner aspect of both thighs. The uterus was the size of a 37 to 38 weeks' gestation. The vertex was dipping into the pelvis.

Fig. 4.—Right labium: lymphatic stasis in the corium. (Low power. Hematoxylin-eosin stain.)

The fetal heartbeat was 140 in the right lower quadrant. On pelvic examination, there was edema of the vulva, especially of the left labium majus. The right labium majus seemed absent and in its place there was granulation tissue. The right side was covered by the left labium majus which was twice as thick as normal. The perineum was relaxed with little scarring. No scar tissue was present in the vagina. The cervix was long, thick, and admitted the tip of a finger.

It was the impression of the visiting staff, in view of previous early deliveries from below and the relatively slight perineal involvement, that the patient should deliver per vaginam.

She was admitted in labor and had a normal spontaneous delivery on May 22, 1953. A routine left mediolateral episiotomy was done and delivery was accomplished without difficulty and without trauma to the site of the vulvar operation. Healing of the episiotomy was by first intention.

The puerperium was uneventful and afebrile.

Comment

Vulvar tuberculosis alone does not appear to be an element of infertility as contrasted to pelvic tuberculosis.[2a] Pelvic genital tuberculous infection is known to spread through the blood and through the lymphatics. Pregnancy, labor, and delivery are known to increase the spread of pelvic genital tuberculosis through any or all of these channels.

Vulvar tuberculosis of the ulcerative type is apparently more serious during pregnancy than the hypertrophic type. In two reported cases of ulcerative tuberculous vulvar lesions in pregnancy one resulted in death and the other in spread. In two cases of hypertrophic tuberculous vulvar lesions, including our case, there was no difficulty in gestation or delivery. Although the number of cases is small, it may be postulated that the lymphatic blockage is so great in the hypertrophic type that massive spread is avoided.

The presence of persistent fistulous sinuses in inguinal lymph nodes should alert the physician to the possibility of vulvar tuberculosis. He should seek diagnosis promptly and institute treatment quickly because of the great danger resulting from spread. Because of the tendency to fistula formation, drainage of lymph nodes should be avoided. Node resection should be performed instead. The treatment of the vulvar lesion depends on its type. Ulcerative lesions respond better to streptomycin, as reported by Charlewood and Proctor[9] and others, while the hypertrophic lesions heal well after surgery. Our patient, although first treated with streptomycin, did not do as well before as after surgery.

The two abstracted cases of ulcerative lesions in pregnancy seem to indicate that fresh tuberculous vulvar lesions arising in pregnancy have a wider spread than hypertrophic lesions. Women with fresh ulcerative tuberculosis of the vulva should be warned against becoming pregnant. Termination of pregnancy should be considered when ulcerative tuberculous vulvar lesions are noted in early pregnancy and cesarean section with tubal ligation considered late in pregnancy.

In our case the lesions were of the hypertrophic type. Not only did they not make the patient infertile, but they did not spread, nor interfere with spontaneous labor. Our decision to permit the patient to deliver per vaginam was based upon (1) good healing after excision, (2) lack of rigid scar tissue, (3) a roomy vagina, and (4) an elastic, uninvolved perineum. The good results apparently justified our decision.

Summary

The literature on tuberculosis of the vulva, a comparatively rare condition, has been reviewed. A case of primary hypertrophic tuberculosis of the vulva, associated with pregnancy, and treated with excision and spontaneous delivery has been presented. No apparent untoward results were noted.

We wish to thank Dr. Vera Dolgopol for the pathological examination, Mr. Milton Marmel for the bacteriological studies, and Mr. Edward Entin for the photography.

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EPINEPHRINE-LIKE SUBSTANCES IN THE BLOOD AND THEIR RELATION TO UTERINE INERTIA*†

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AT THE Johns Hopkins and the Sinai Hospitals in Baltimore, Kaiser and Harris[1] and later Kaiser[2] administered minute amounts (2.5 to 4 μg per minute) of epinephrine intravenously by drip infusions and noted that uterine motility was inhibited in women during labor. These investigators pointed out that "In difficult labor there is a state of emotional stress which may well induce excessive secretion of endogenous Adrenalin. The disorganization of patterns of uterine activity observed in inertial labor resembles in many respects that induced, for brief periods, by exogenous Adrenalin."[1]

It has long been felt that part of the pain syndrome involves the production of endogenous epinephrine. Moreover, Hardy[3] reported that women with a low pain threshold, who are tense and fearful of labor, may have either inhibited or irregular uterine contractions, probably because of endogenous epinephrine. Thus the first and second stages of labor may be prolonged, giving rise to uterine inertia.

It was, therefore, felt that, in view of the clinical evidence and the work of Kaiser and Harris previously noted, epinephrine blood levels, if determinable, should demonstrate differences between patients in normal labor, patients with a fearful approach to labor, and patients in labor with inertia.

Attempt was made, therefore, to determine the blood levels of epinephrine in unselected patients who had normal labors, or labors with apprehension or inertia. The method for the determination of epinephrine levels is herewith described. Determinations were made on 10 patients who had normal labors, 18 patients who were fearful of labor, and 5 who had labors of an inertial type.

Method of Determination of Epinephrine Levels

Perusal of the literature, recently reviewed by Pekkarinen,[4] discloses that for the past half century investigators have been seeking suitable methods for the determination of epinephrine by both biological and chemical procedures. Although the chemical methods are more specific and precise, the biological methods are more sensitive and can be used to determine minute quantities of epinephrine. Because such small amounts of epinephrine produced the effects described by Kaiser and Harris, the chemical methods (along which lines we had first embarked) were discarded and a more sensitive, although more difficult and time-

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consuming, biological procedure was adopted. A modification of the very sensitive bioassay method of García de Jalón, Bayo Bayo, and García de Jalón[5] was used.

Collection of Blood.—

Venous blood is drawn from the patient from the antecubital vein immediately following a uterine contraction, using a sterile syringe which has been refrigerated. Coagulation of blood is delayed with the aid of minute quantities of heparin. The blood, once drawn into the syringe, is transferred immediately to a dry 15 ml. centrifuge tube jacketed by a 50 ml. centrifuge tube with water-soaked packing in between both tubes which has been frozen by previous refrigeration. The warmth of the blood permits separation of the 15 ml. centrifuge tube in which the cellular elements are rapidly spun down in a refrigerated centrifuge. The plasma is then transferred with dry, chilled pipettes to a refrigerated test tube which is then placed quickly in the refrigerator until tested.

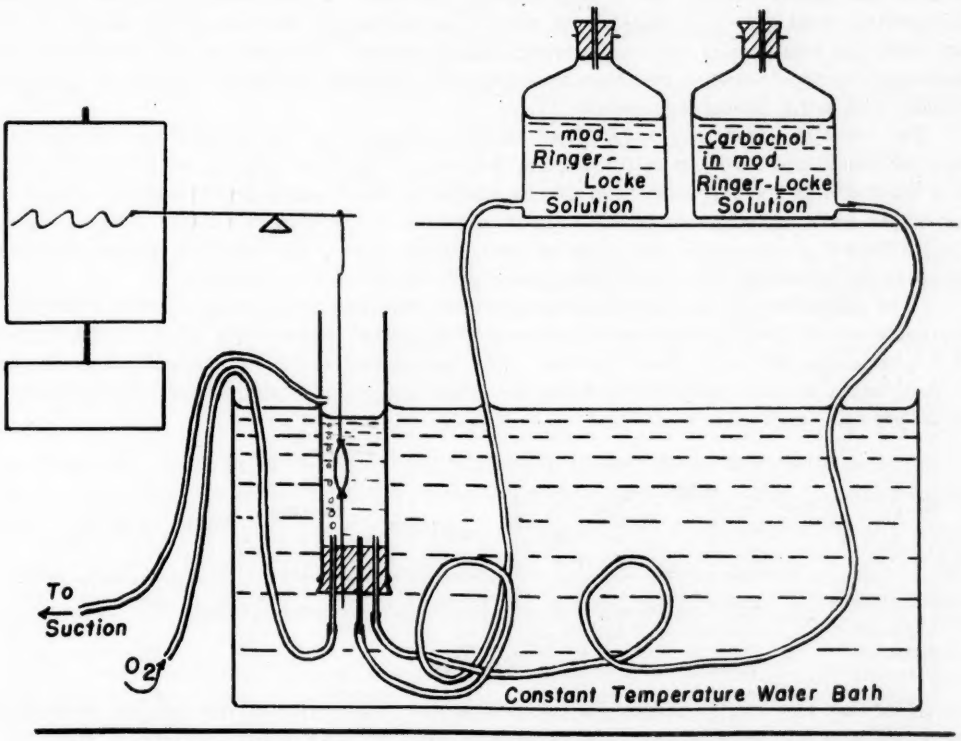

Fig. 1.—Diagrammatic representation of tissue bath as used in procedures.

Assay.—

Samples of plasma extracts are compared with solutions of synthetic l-epinephrine (Sterling Winthrop). The rat's uterus, or only one horn of it, is suspended in a small tissue bath (3 to 5 ml.) in a solution of the following composition:

NaCl	9.0 Gm./L.
KCL	0.42 Gm./L.
$CaCl_2$	0.06 Gm./L.
$NaHCO_3$	0.20 Gm./L.
Glucose	0.50 Gm./L.

The tissue bath is kept suspended in a constant temperature water bath at 25° C. Contractions are produced every two minutes by a choline ester, and the assay depends upon the

inhibition of the contractions by the l-epinephrine in the known solutions or the epinephrine-like substances of the plasma under assay. The isotonic contractions were recorded on the kymograph, using a simple lever with a 1:4 ratio.

A similar solution containing carbachol is used to replace the solution of the bath every two minutes and allowed to perfuse the uterus for 30 seconds, causing it to contract. Carbachol is used in place of acetylcholine because of its greater stability. After 30 seconds, the carbachol solution is then replaced by the original solution. The concentration of carbachol is 1.0 μg per milliliter. The additions of solutions were timed accurately with a stopwatch.

The solutions are introduced slowly through the bottom of the tissue bath and are suctioned off at the top through a capillary tube connected to a vacuum line. Solutions of l-epinephrine of known concentration or plasma are added one minute before the inflow of carbachol. The solutions are allowed to flow for 15 seconds when the bath contents are changed. The solutions are brought to the temperature of the bath by allowing the solutions to flow slowly through the tubing which is immersed in the constant temperature bath. Polyethylene tubing is used exclusively and no metal except platinum is permitted in contact with the solutions in order to prevent side reactions. The pH of the solutions in the tissue bath is kept constant by frequent changes of solutions and is maintained at 7.4, being checked with a La Motte comparator.

The uteri of older rats were found to be preferable, as the uteri from younger rats were too small and weak, in spite of using both horns together, side by side. In older rats, it is advisable to use only one horn of the uterus to avoid incoordinate activity of the two horns. In addition, only rats in the nonestrous phase of the cycle are used. Vaginal smears are performed to determine the stage of the estrous cycle. The uteri of estrous rats were found to be unreliable and their spontaneous activity difficult to control.

The differences in the heights of contractions with and without the inhibiting action of l-epinephrine or blood epinephrine substances were plotted against the known concentrations of l-epinephrine for each determination. The concentration of the epinephrine substances in the plasma is then extrapolated from the graph and read as micrograms per milliliter of l-epinephrine.

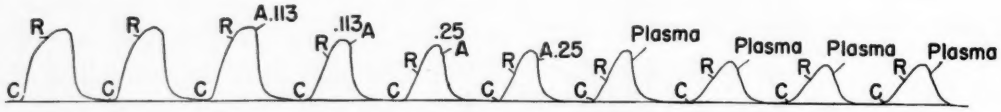

Fig. 2.—Photograph of typical kymographic tracing.

Results

During the early attempts to determine the epinephrine levels, specimens were drawn at any stage during labor and it was soon apparent that if a measurable level of epinephrine was to be obtained specimens had to be drawn after a cervical dilatation of 5 to 6 cm. Therefore, all specimens in this series were obtained after a dilatation of 5 to 6 cm. or more, but prior to the administration of Demerol or other analgesics.

The blood specimens were drawn from patients with normally progressing labors, apprehensive patients with moderately painful labors, and patients with inertial labors. The specimens were labeled with P_1, P_2, P_3, etc., and dated. The patients' names, dates, and identifying symbols were recorded separately. The determinations were then carried out by one of the authors with no effort to identify the specimen to correlate the kymographic tracings with the clinical picture until after the kymographic tracings were completed. Although the determinations were made very soon after the specimens were drawn (within a few hours), measurements of the heights of contraction and drawing of graphs

were not carried out for some time thereafter. Specimens were tested soon after being drawn to prevent loss or decomposition of the epinephrine substances.

Of the 10 patients with normally progressing labors (Table I) only 3 had detectable epinephrine levels by this test. The labors were relatively short. Only 2 patients received Demerol for pain, and 2 had been given Nembutal early in labor. One patient had mild pre-eclampsia and had been treated with magnesium sulfate and Luminal sodium. The two patients who received Demerol for pain and one who had received Nembutal early in labor had the detectable epinephrine-substance levels.

The 18 apprehensive patients with moderately painful labors had moderately prolonged labors in comparison with the previous group. Measurable

TABLE I. DATA FROM WOMEN IN NORMALLY PROGRESSING LABOR

CASE NO.	AGE	PARITY	HOURS IN FIRST STAGE	MINUTES IN SECOND STAGE	TOTAL HOURS, FIRST AND SECOND STAGES	EPINEPHRINE SUBSTANCE LEVEL (μG/ML.)	MEDICATIONS
6837	16	0	21	58	21 58/60	0.0000	None
6845	21	i	12	21	12 21/60	0.0000	None
6867	24	0	9 4/60	15	9 19/60	0.0235	Nembutal
6863	19	0	11 ¼	10	11 25/60	0.0000	None
6861	18	0	7	40	7 2/3	0.0000	None
6748	38	ix	2	10	2 10/60	0.0000	Pre-eclampsia routine
105	36	i	3 ½	15	3 45/60	0.0520	Demerol
119	23	i	6	5	6 5/60	0.0330	Demerol
4181	33	ii	6 ½	5	6 35/60	0.0000	None
5337	25	i	6	3	6 3/60	0.0000	Nembutal

Variance = 3.52×10^{-4}.
Standard deviation = 0.0188.
Standard error of mean = 0.0059.
t = 1.86.

TABLE II. DATA FROM WOMEN WITH PROLONGED LABORS, MOST REQUIRING SEDATION

CASE NO.	AGE	PARITY	HOURS IN FIRST STAGE	MINUTES IN SECOND STAGE	TOTAL HOURS, FIRST AND SECOND STAGES	EPINEPHRINE SUBSTANCE LEVEL (μG/ML.)	MEDICATIONS
6738	37	vi	14	25	14 25/60	0.0155	Demerol
6744	20	0	10	30	10 ½	0.0220	Demerol
135	32	x	5	1	5 1/60	0.0690	Demerol
136	29	v	10½	5	10 35/60	0.1110	Demerol
1807	24	ii	6½	10	6 40/60	0.0140	Demerol
1812	20	0	20	15	20 ¼	0.0140	Demerol
2661	25	v	9	10	9 10/60	0.0330	Demerol
6196	19	ii	8½	20	8 50/60	0.0030	Demerol
6210	18	i	10	10	10 10/60	0.0160	Demerol
5313	32	ii	12	16	12 16/60	0.0080	None
5293	17	i	10	15	10 ¼	0.0190	None
13	21	i	3	5	3 5/60	0.0820	Demerol
179458	27	v	12½	5	12 35/60	0.0590	Demerol
4252	27	i	12	20	12 20/60	0.0670	Demerol
4264	29	vi	9⅓	5	9 25/60	0.0670	Demerol
4265	21	0	20½	30	21	0.0230	Demerol
5263	28	i	11¼	30	11 ¾	0.0020	Demerol
5564	32	0	Cesarean section at 7 cm. Fetopelvic disproportion			0.0180	Demerol

Variance = 10.6×10^{-4}.
Standard deviation = 0.0325.
Standard error of mean = 0.0077.
t = 4.52.

levels of epinephrine substances were determined and all but 2 required analgesics for control of pain. These two did not receive analgesia due to an oversight in carrying out the orders of the attending doctor. One of these patients was delivered by cesarean section at 7 cm. dilatation because of fetopelvic disproportion.

The 5 patients with inertial labors had even more prolonged labors, which would probably have been longer had the uterine contractions not been stimulated by intravenously administered Pitocin solution. All specimens were drawn prior to the administration of Pitocin and all disclosed even higher epinephrine-substance levels in the blood than in the second group of patients previously described.

Table IV shows the average values for each of these groups.

The sensitivity for this test was determined as 0.0119 μg per milliliter with standard error of the mean of 0.0038. In comparing the mean values for the three groups it becomes apparent that the normal group has so low a level of epinephrine-like substances that it was not possible to measure a significant amount by this procedure. On the other hand, the apprehensive group had a greater amount detectable and the inertial group a much more marked level.

TABLE III. DATA FROM WOMEN WITH UTERINE INERTIA, TERMINATED BY INFUSION OF PITOCIN

CASE NO.	AGE	PARITY	HOURS IN FIRST STAGE	MINUTES IN SECOND STAGE	TOTAL HOURS, FIRST AND SECOND STAGES	EPINEPHRINE SUBSTANCE LEVEL (μG/ML.)	MEDICATIONS
6885	34	0	21½	150	24	0.1080	Demerol I.V. Pitocin
29	29	0	12¼	90	13¾	0.1520	Demerol I.V. Pitocin
2641	26	ii	13½	45	14¼	0.1540	Demerol I.V. Pitocin
3085	21	i	7½	15	7¾	0.1620	Demerol I.V. Pitocin
3646	32	ii	7	5	7 1/12	0.1660	Demerol I.V. Pitocin

Variance = 5.43×10^{-4}.
Standard deviation = 0.0233.
Standard error of mean = 0.0104.
t = 14.27.

TABLE IV. SUMMARY OF AVERAGES FROM TABLES I, II, AND III

PATIENT CLASSIFICATION	AVERAGE TOTAL LABOR, FIRST AND SECOND STAGES	EPINEPHRINE SUBSTANCES (μG/ML) (MEAN VALUE)	STANDARD ERROR OF MEAN	TREATMENT
Normal	8 hrs., 43 min.	0.0109	0.0059	Nursing Care
Fearful	11 hrs., 15 min.	0.0347	0.0077	Sedation
Inertial	13 hrs., 17 min.	0.1484	0.0104	Sedation I.V. Pitocin
	Mean sensitivity	0.0119	0.0038	

Comment

This report is a preliminary one, and our series is small. We believe we have succeeded in demonstrating significant blood levels of epinephrine substances present in apprehensive patients with moderately painful labors and even higher levels in patients with inertial labors. We also have demonstrated that the nonfearful patient has no appreciable or identifiable blood level of epinephrine substances.

Again we must stress that these determinations were done as unknowns and the results were not correlated with the cases until after all information had been obtained.

It is obvious that the correlation of these facts with the effects of uterine contraction could be demonstrated by the external tokodynamometer for contraction organization and intraovular pressures for effective force of contractions. This study could be enhanced by studying similarly the effects of sedatives, regional anesthetics, and possibly certain adrenolytics on uterine contractions during labor. With these two important factors correlated, we might be able to shed further light on the still perplexing problem of uterine inertia.

We wish to acknowledge that this problem was suggested, initiated, and carefully guided by Dr. Samuel R. M. Reynolds, Acting Director of the Carnegie Institution of Washington, Baltimore, Maryland, and that the work was greatly aided by the late Dr. Samuel Lubin, then Director of the Department of Obstetrics and Gynecology at Cumberland Hospital and Director of the Kate Lubin Research Foundation, Inc.

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THE EFFECT OF URECHOLINE ON THE POSTPARTUM UTERUS*

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THE original intent of the method used in this investigation was to study the effect of drugs which might produce relaxation of the uterine musculature. Our attention was diverted for the moment to the effect of Urecholine (urethan of beta-methylcholine chloride)† on the uterine musculature as a result of the extensive studies of its gastrointestinal effects conducted by Meyer and his associates[1] at the Cook County Hospital. Their studies indicated that Urecholine is a potent parasympathomimetic drug with relatively low toxicity and no serious side effects. It produces an increase in gastric and intestinal motility and causes contraction of the urinary bladder.

This investigation was conducted by recording the effect of Urecholine on the normal human postpartum uterus immediately after delivery of the placenta.

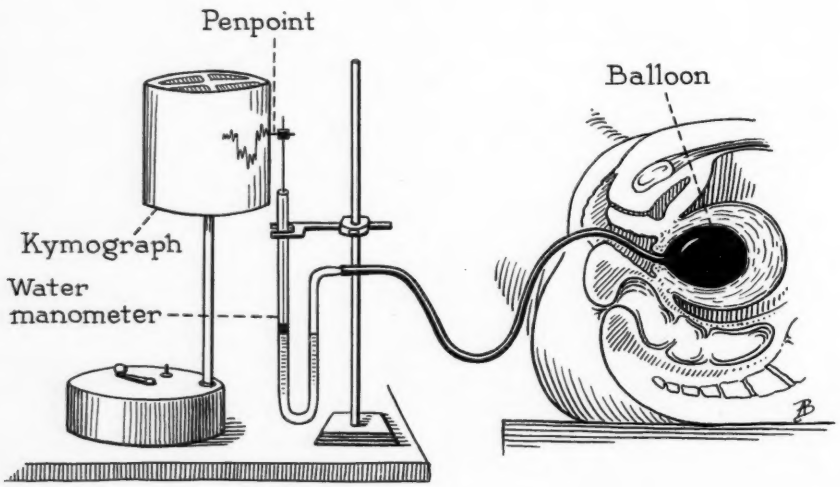

Fig. 1.

The apparatus used consisted of an air-filled rubber balloon which was placed inside the uterine cavity (Fig. 1). The effect of the uterine contractions was transmitted from the balloon to a water manometer. The fluctuations of the water in the manometer were recorded by means of a float to which

*This investigation was supported by a research grant from the Dr. Jerome D. Solomon Research Foundation, Hektoen Institute for Medical Research.

†The drug was supplied by Merck and Co., Rahway, N. J.

a writing point was attached and adjusted to a kymograph. The pressure in the balloon was kept constant by introducing the same amount of air in the system (20 c.c.) with each experiment.

We recorded and studied the normal activity of the postpartum uterus with this apparatus prior to the actual pharmacological investigation in order to be cognizant of the normal pattern.

The patients studied were at term with normal labors. No medication (analgesics or oxytocics) was administered during or after labor. Delivery was accomplished as indicated with the use of local infiltration or pudendal nerve block using 1 per cent procaine.

A composite study of the normal graphs over a period of 4 hours after delivery of the placenta indicates that the uterine contraction has a rapid increment (about 15 per cent of the total length of the contraction), maintains its maximum contraction about 35 per cent of the total, and has a gradual decrement (about 50 per cent).

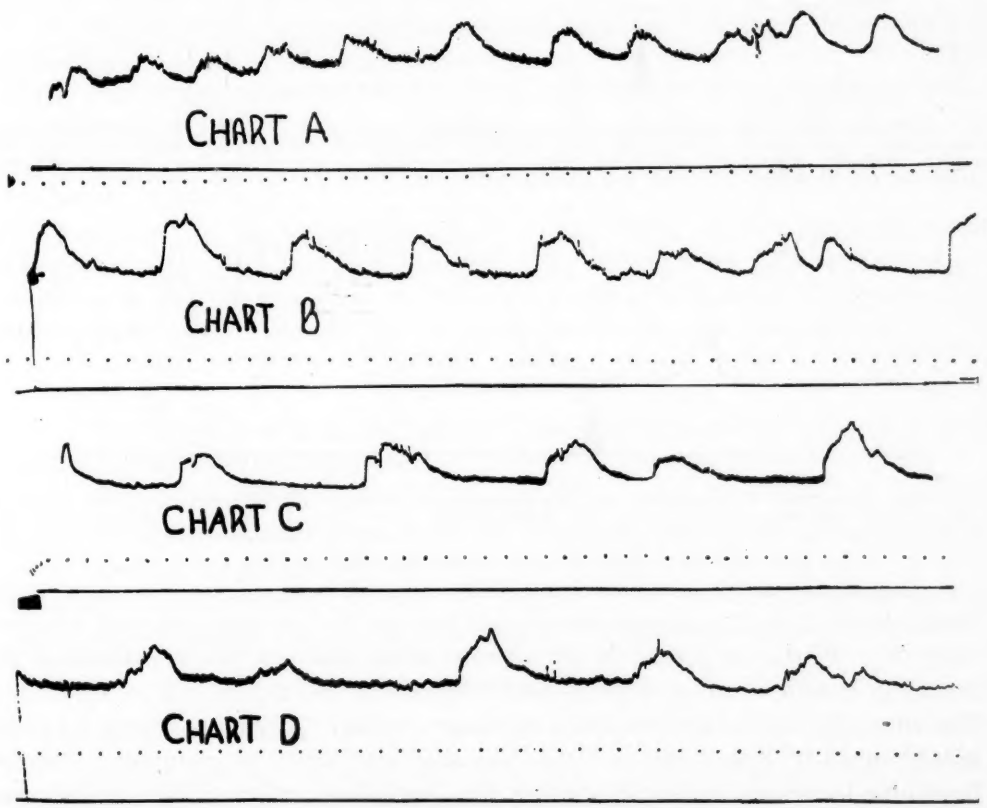

Fig. 2.—Recording of normal postpartum uterine contractions. (Dots occur at one-minute intervals.)

Chart A, Recordings begin immediately after delivery of the placenta.

Chart B, Continuation of *A.* Begins 50 minutes after delivery of the placenta.

Chart C, Continuation of *B.* Begins one hour and 50 minutes after delivery of the placenta.

Chart D, Continuation of *C.* Begins 2 hours and 45 minutes after delivery of the placenta.

The characteristics of successive uterine contractions in any one individual may vary to a small extent. There may be major variations between individuals. If there is uterine inertia before delivery, the same characteristics will be exhibited during the postpartum period.

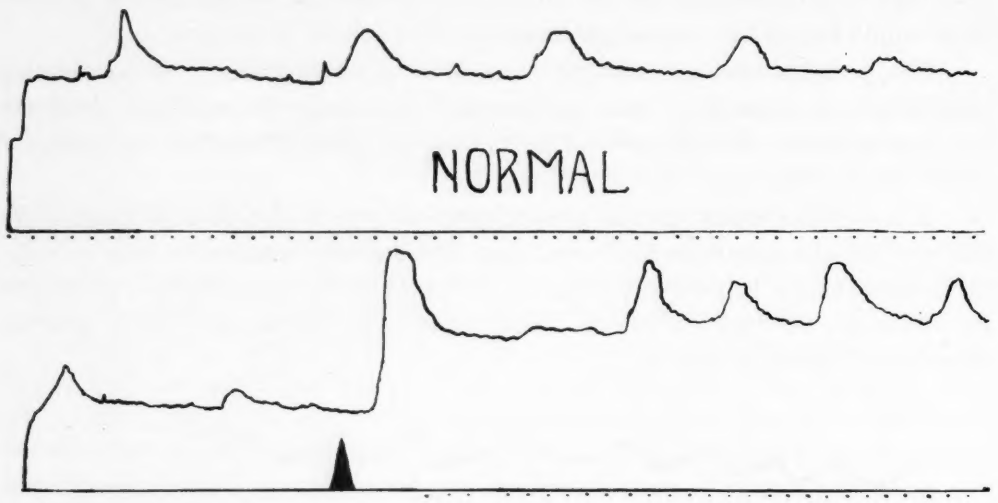

Fig. 3.—Effect of Urecholine on the postpartum activity of the uterus. (Dots occur at one-minute intervals.) The upper recording is that of uterine activity approximately two hours after delivery of the placenta. The lower recording is a continuation of the upper and indicates the response following the administration of 10 mg. Urecholine subcutaneously.

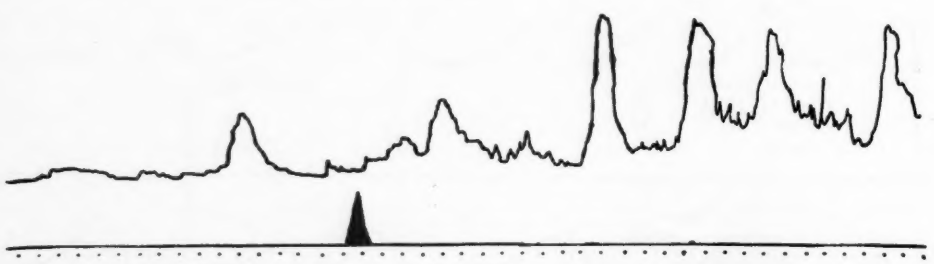

Fig. 4.—Effect of Urecholine on the postpartum activity of the uterus. (Dots occur at one-minute intervals.) Recording of postpartum (two hours) uterine activity and the response following the administration of 10 mg. of Urecholine subcutaneously.

The initial uterine contractions following delivery of the placenta occur about every 2 to 3 minutes and persist for one to one and one-half minutes (Fig. 2). Within a period of 30 minutes after delivery, the contractions increase in length to three minutes and decrease in frequency to 5 to 6 minutes. The intensity of the contractions increases (where 1.5 cm. of water was displaced initially, 2 to 3 cm. of water was displaced after 30 minutes). Uterine tone also increases gradually during this period as indicated by the increase in pressure within the system (where 3.5 cm. had existed between the base line and the actual recording of the uterus in diastole, there was 6 cm. after 30 minutes).

The changes in characteristics of the uterine contractions occurred more slowly after the initial 30 minutes. After 3 hours, the contractions occurred

on an average of 8 to 10 minutes and persisted for 3 to 4 minutes. The intensity of the contractions (the uterine tone) remained approximately the same as had occurred 30 minutes after delivery.

The effect of Urecholine on the contractions of the postpartum uterus was studied by using the drug orally and subcutaneously in varying doses.

The effect of the oral administration of dosages of 10 mg., 20 mg., and 30 mg. of Urecholine was recorded (one case for each of these dosages) and studied. The results indicated no significant changes on the kymographic recording.

Five recordings were made and studied in which 10 mg. of Urecholine was administered subcutaneously (Figs. 3 and 4). The effect was noted on the kymographic recording in approximately 7 minutes after administration. The effects were:

1. An increase in uterine tone in 4 instances.
2. The frequency of uterine contractions increased in 4 instances. The uterine contractions were not clearly defined on the fifth recording and therefore interpretation was not attempted.
3. The strength of the uterine contractions was definitely increased in 2 recordings and unaltered in the remaining 3.
4. The length of the contractions was not altered. In one instance, where the contractions had lasted for 7 minutes and occurred every 9 minutes, the contractions were altered so that they occurred every 4 minutes and lasted 3 minutes.

The effect of the administration of 15 mg. of Urecholine subcutaneously was recorded and studied in 3 patients. The results were similar to those obtained with the 10 mg. dose but the incidence of side effects (perspiration, flushing, abdominal cramps) was more frequent and more pronounced.

Conclusions

1. The normal postpartum uterus continues to contract according to a pattern as recorded and described.
2. The oral administration of Urecholine has no effect upon the contractions of the postpartum uterus.
3. The subcutaneous administration of Urecholine (10 mg. and 15 mg.) increases the incidence of the uterine contractions and increases the uterine tone. An occasional increase in strength of contractions was noted.

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FORTY YEARS OF POSTPITUITARY EXTRACT IN OBSTETRICS

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THE importance of the initial impulse that a fascinating experimental observation may inspire for its application to spheres of considerable practical interest is forcefully illustrated by the mosaic of significant advances which resulted from the report by H. H. Dale[1] of vigorous contractions of the virgin guinea pig's uterus suspended in a neutral solution, induced by the addition of postpituitary extract. Factual background data form the basis of the present attempt of an objective evaluation of the merits of postpituitary preparations as a therapeutic standby, while an exhaustive review of the subject is not in the scope of this survey.

In planned experiments conducted in our laboratory, the reduction to one-fifth and later to one-tenth the amount of postpituitary extract originally used elicited a new pattern of contractions of the suspended uterine horn, characterized by sustained rhythmic contractions occurring in regular intervals similar to the phenomena during the first and second stages of labor. As a result of this observation an active program of using postpituitary extract *during labor* was initiated, and our first report in January, 1911, described the dramatic changes occurring in cases of uterine inertia following the subcutaneous administration of the drug, and the termination of labor in a remarkably short period of time. A note concerning the efficacy of the drug, both in overcoming atony of the puerperal urinary bladder and in inducing labor at term was added.[2a] The appearance of more than 100 confirmatory publications during the next two years attested the outstanding acceptance of the new successful attack on the major problem of uterine inertia during labor. It was inevitable, however, that the optimism engendered by these reports particularly emphasizing the uniqueness inherent in postpituitary action during labor would promote its abuse. In order to forestall the indiscriminate use of the drug, our second report tended to determine precisely the indications and contraindications on the basis of our experience and the opinions of the profession advanced during the seven-year period. Here, it was stated categorically that a thorough examination is indispensable in order to rule out cephalopelvic disproportion and abnormal presentations as possible causes of delay and, specifically, that the administration of postpituitary extract was not the proper means of overcoming the difficulties presented by cervical dystocia or a rigid perineum. For the treatment of placenta previa lateralis, rupture of the membranes followed by the injection of 0.5 c.c. of postpituitary extract was advocated by reason of the stimulation of uterine contractions which force the descent of the presenting part and its continuous pressure against the separated margin of the placenta.[2c]

Motivated by the desideratum of an immediate effect in cases of emergency, the introduction of the *intravenous* administration of postpituitary extract marked its second major step. The dramatic uterine response to 2 to 3 minims of the extract diluted with 2 c.c. of saline brought the advantages of the intravenous route into prominence. The incentive of the new procedure encouraged its successful employment during labor in cases of uterine inertia which had exhibited a feeble response to the subcutaneous administration of the drug.[2b] Significantly, the instantaneous and dramatic effect obtained in acute postpartum atony made the intravenous route the method of choice. In point of fact, ever since the introduction of the intravenous administration of the drug, I have dispensed with the method of packing the uterus and other procedures of questionable value. In order to ensure a lasting effect, 1 c.c. of postpituitary extract is given subcutaneously or intramuscularly three minutes after the first intravenous dose. Rarely do I resort to ergot preparations, particularly in view of the recent analysis of Sheehan and Summers[4] pointing to the fact that necrotic areas in the anterior lobe of the hypophysis occurred in the wake of excessive postpartum blood loss in some patients who had received injections of ergot. A special article summarized the dominant interest awakened by the introduction of the intravenous administration of postpituitary extract and highlighted the indications.[2,f] Attention was called to the dynamic restoration of tone in the atonic ureter during gestation and the marked improvement noted in the course of pyelitis following the administration of the drug.[2f] The effect of intravenous postpituitary extract on the exposed pregnant uterus manifests itself by the occurrence of pale bands in the midline and concurrently in the region of the insertion of the tubes, involving formations which structurally resemble the bundle of His and are looked upon as the pacemaker of the uterine contractions. The elective stimulating effect of postpituitary extract on the subperitoneal specialized muscle from which the waves of contraction spread to the uterine muscle proper was obvious.[2c] Our report was corroborated by the subsequent experimental results of Hartmann and Koff[3] in Rhesus monkeys.

The nasal administration of postpituitary extraction for the induction of labor is still standard procedure in several institutions. The possibility of withdrawing the drug whenever the uterine action becomes too violent constitutes the advantage of the method.[2d] The injection of postpituitary extract into the substance of the uterine cervix prior to the removal of remnants of placental fragments in abortion served to protect the uterine wall against undue injury, by reason of the vigorous uterine contraction produced.[2g]

Variations in individual susceptibility to the drug and even refractoriness occurred in a certain proportion of cases. Underdevelopment of the uterine musculature is generally considered a frequent cause. Correlation with defective development of the specialized muscle system in elderly primiparas was mentioned in our description of the structure.[2e] Inadequate knowledge of the part played in the regulation of uterine activity by the pelvic ganglion (Frankenhäuser) precludes any pertinent discussion of its abnormal action in

uterine atony. Attention, however, is directed toward the possibility of inhibitory hypothalamic influences.

The three decades following the introduction of postpituitary extract into the obstetrical armamentarium were a period of contrast and fluctuating appreciation of the benefits accruing from the utilization of the drug in prolonged labor, with dissenters predominant in this country. In the light of the acute divergence of expert opinion, great credit is accorded the authoritative statement by Duncan E. Reid,[5] in 1946, that "posterior pituitary extract can be administered safely during labor without undue harm to either mother or baby." The report based on an impressive experience stresses the sharp reduction in operative interference. The major impact of Reid's presentation served momentarily to alter the general attitude toward the use of postpituitary extract during labor to a notable extent and represents an eloquent vindication of its administration during labor.

Additional impetus was given to the subject by the advocacy of the administration of small doses of postpituitary extract by the continuous intravenous use of pitocin (Theobald[6]). The sustained effect during labor and its controllability are quoted as the essential features of the method. The warning that in cases of excessive sensitivity to the drug the infusion should be interrupted and that adequate supervision is necessary whenever the method is applied to multiparas accords well with the admonition stressed in my previous publications. *Nil prodest, quod non possit laedere idem* (Ovid). Personally, in acute postpartum bleeding I prefer the intravenous administration of 2 to 3 minims of postpituitary extract diluted with 2 c.c. of saline as the most dependable method of procuring an immediate tetanic uterine contraction. In uterine inertia during labor, the infusion of adequate amounts of 5 per cent glucose apparently restores the reactivity of the uterine musculature exhausted by the long duration of labor to small amounts of the drug and, thus, represents supportive treatment. In my hands, in addition to the infusion of glucose, the early administration by the subcutaneous route of 0.25 c.c. Pitocin, repeated at twenty-minute intervals until sustained rhythmic uterine contractions ensue, has given entirely satisfactory results in the treatment of uterine inertia during labor.

It will not be amiss to add the concluding remark that it was the interest in postpituitary activity which initiated our efforts to elucidate the part played by the posterior pituitary in the origin of pregnancy toxemia.[2h] The recent demonstration of the presence of large amounts of phenylalanine in the urinary excretion in toxemia represents an important addition in view of the recognition of this amino acid as an essential component of Pitressin.

Comment

The accretions of knowledge during the past four decades concerning the merits of postpituitary oxytocics and their vital role in the treatment of uterine inertia during labor and in the immediate postpartum period are discussed from a present-day perspective.

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REDUCING THE RISK OF TOTAL ABDOMINAL HYSTERECTOMY*

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GYNECOLOGISTS now fairly universally agree that if hysterectomy is to be performed, complete removal of the uterus is desirable and possible, practically without exception. The risk of total hysterectomy has been steadily decreasing through the past two decades, so that now an operative mortality rate greater than 2 per cent is exceptional. It is not unusual, however, for the postoperative morbidity rate, which is an index of the risk to the patient's life, to be 35 per cent. In the past seven years, numerous studies dealing with and seeking to prevent postoperative morbidity have been published.[1-6]

As outlined so well by Johnson and Burman,[5] the morbidity rate following total abdominal hysterectomy varies generally between 27 and 41 per cent. The criteria for diagnosing morbidity vary somewhat from author to author, some considering the temperature beginning on the first postoperative day, others beginning twenty-four hours after operation, and still others beginning after the first postoperative day. Our criteria are similiar to, but not identical with, those of the Joint Committee on Maternal Welfare,[12] being an oral temperature of 100.4° F. or over, on any two consecutive days after the first postoperative day, temperatures to be taken four times daily.

Practically all studies on morbidity emphasize the importance of exact surgical technique. Some of the most recent studies emphasize the importance of the preoperative vaginal preparation. Cron, Stauffer, and Paegel,[7] studying a rather large series, found that the use of a Zephiran vaginal pack and a penicillin vaginal suppository reduced their morbidity rate for total abdominal hysterectomy from 45 to 21 per cent. Several other studies[8, 9, 10] verify the importance of careful preoperative vaginal preparation. Unfortunately, some of these studies combine the results in vaginal hysterectomy and in minor procedures, so that the presumed beneficial results with total abdominal hysterectomy are obscured.

A recent study of 518 consecutive hysterectomies from this hospital,[6] of which 483 were total abdominal hysterectomies, revealed that 36 per cent of the latter patients had morbid postoperative courses. The outstanding cause of the fever was pelvic infection with or without abscess or peritonitis. We have become accustomed to designating this complication "parametritis," because the seat of the inflammatory process is the pedicles of the cardinal ligaments and the closely adjacent parametrial structures (uterosacral pedicles, pedicles of the uterine vessels, the perivaginal fascia, broad ligaments, and

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adnexal pedicles). We believe that the cause of the elevated temperature is often wrongly attributed to cystitis, because of the proximity of the bladder and the frequent finding of pus cells in the urine. Very often we have noted that a rapid return of the body temperature to normal is associated with a sudden increase in the reddish-brown, malodorous vaginal discharge which undoubtedly had been loculated in the subvesical parametrial space.

With due attention to the foregoing considerations, we formulated a study whereby, with the cooperation of the Gynecological Group of Ellis Hospital, a routine for total abdominal hysterectomies was established. All factors which could contribute to elevating postoperative temperature were analyzed. The surgical technique was perfected and standardized as completely as possible. The preoperative preparation was standardized, and patients were taken at random in the various groups. The degree of intrinsic risk was evaluated for each patient. The postoperative care was standardized. The only significant difference among the several groups of patients was the type of preoperative vaginal preparation given. The results were compared after about forty patients were treated by each method, and the method affording the best results was subjected to a second test, including a second group of forty patients. The results were then analyzed statistically.

Basic Considerations

Certain constant and variable factors apply to each of the operations reported in this series. The constant factors are: the preoperative enema; preoperative catheterization; the skin preparation; the incision (low midline as a rule; occasionally a Pfannenstiel); the use of dry skin towels; catgut technique; fresh gowns, gloves, drapes, and instruments for closure of the abdominal wound; and the withholding of antibiotics before development of morbidity.

The variable factors to be considered in each of the operations in this series are: the patient; the surgeon; the preoperative vaginal preparation; ligation of bleeding points (some operators being meticulous, others less particular); insertion of drains in the vault (a drain was used in practically every case in this series; in some instances the cul-de-sac was drained as well as the subvesical area); the technique of suturing the vaginal cuff; treatment of the adnexa; technique of peritonization; details of wound closure; appendectomy; and coincidental vaginal plastic operations.

A most important variable factor in any major operation is the patient. In this series, we have graded patients according to surgical risk. Patients with the least potential risk were placed in Class I, those with the greatest risk, in Class IV. The grade of risk was advanced one class for each of the following factors: a subcutaneous fatty layer more than 4 cm. thick; extensive peritoneal adhesions; endometriosis of the pelvic peritoneum of moderate or marked degree; large myomas; the presence of pelvic malignancy; very severe cervicitis; chronic inflammation of the tubes or pelvic peritoneum; uterine bleeding at the time of operation; the presence of diabetes mellitus;

and the coincidental performance of vaginal plastic procedures. As will be seen, the distribution of patient risk in each group is approximately equal, making statistical evaluation simpler.

The most important extraneous risks must admittedly be introduced at the time of operation. These will be considered now. Catheterization, even by a registered nurse, always carries the risk of contamination of the bladder with subsequent serious upper urinary tract infection. The hands, nose, throat, and hair of the operator and assistants are always possible sources of contamination of the field. The skin cannot be sterilized; our preparation consists of applications of Pyxol* and tincture of Zephiran.† The laparotomy drapes can be a source of contamination by inadequate sterilization or by becoming moistened with blood or other liquids. Instruments and sponges can be unsterile. The vagina can hardly be sterilized. Poor hemostasis can lead to the formation of pyrogenic hematomas. Tissues can be isolated from their blood supply by poor surgical technique. Excessive trauma necessitates absorption of small or large portions of crushed tissue, with consequent pyrexia. The risk of perforation of bowel, bladder, or ureter constantly besets the gynecologist. The choice of suture material is of some importance.

There will always be a certain percentage of hysterectomies that are performed without adequate indications. This percentage will of course affect the results in any series, because the pathology present in such cases is minimal, and therefore the risk is less. We pride ourselves on feeling that such procedures are at a minimum in this series.

Technique

Several different routines for vaginal preparation were tested, with about 40 patients in each group. After the completion of this series, the preparation giving the best results (Type IV, Table IV) was retested in another series of about 40 patients.

The alcohol and Pyxol basins were proved to be sterile. The skin was always prepared by the resident. Dry skin towels were always used, and care was taken to cover the wound edges with these towels before insertion of the self-retaining retractor. After completion of the intraperitoneal procedures, including insertion of the drain and appendectomy if necessary, the skin towels were removed, gowns and gloves were changed by surgeon, assistants, and nurse, fresh towels were applied around the wound, and a fresh set of sterile instruments was used for closure.

The technique of hysterectomy was essentially that described by Cornell and co-workers.[6] Hemostasis should be emphasized, and trauma minimized. The most important arteries encountered, in decreasing order of importance, are the cervicovaginal branches of the uterine, the appendiceal, the ovarian, and finally, the uterine. Peritonization is important in the prevention of adhesions, as emphasized by Phaneuf.[11] Our closure technique was continuous chromic No. 1 sutures for the peritoneum, two or three pieces of continuous chromic No. 1 catgut for the anterior rectus sheath (with no eviscerations), continuous chromic No. 000 for Scarpa's fascia and subcutaneous tissue, and Michel clips for the skin.

*Pyxol is a 2 per cent solution of concentrated Pyxol (a coal-tar derivative) in a mixture of three parts 95 per cent alcohol and two parts acetone.

†Zephiran is an antiseptic quaternary ammonium salt.
Admittedly there are many completely satisfactory methods of preparing the skin.

After the operation, hydration was maintained, usually orally, but often with intravenous liquids. Coughing, deep breathing, and moving about in bed were encouraged. The catheter was left in place during the first night to prevent bladder distention. All patients were ambulated on the first postoperative day. Skin clips and vaginal drain were removed on the fifth day. The patient usually was discharged on the seventh day and a stay of more than ten days was unusual.

Material

The patients in this series were divided into groups according to the type of vaginal preparation:

Type 1, cotton vaginal tampon with cervical end soaked in 10 ml. of 5 per cent Sulfamylon* inserted the afternoon before operation.

Type 2, dry cotton vaginal tampon inserted the afternoon before operation.

Type 3, disinfection in operating room with tincture of Zephiran and dry sponging.

Type 4, penicillin-streptomycin suppository† inserted in posterior fornix the afternoon before operation.

Type 5, no pelvic examination in hospital, no preoperative vaginal preparation.

The results are presented in Tables I to V.

In the group with Type 1 preparation, one patient had pyelitis, which is discounted since the surgical procedure per se was not to blame, and one patient had a wound infection, which is preventable, therefore is included in the net morbidity. All other morbidity was apparently due to "parametritis."

In the group with Type 2 preparation, 2 patients had pulmonary atelectasis, and one had a wound infection. The former are discounted in the net rate.

TABLE I. VAGINAL PREPARATION, TYPE 1. 41 PATIENTS

OPERATIVE RISK, CLASS	NUMBER OF PATIENTS	NUMBER MORBID	PATIENTS MORBID DUE TO PELVIC COMPLICATION
I	6	0	0
II	21	3	2
III	12	4	4
IV	2	1	1
Gross morbidity rate 20%		Net morbidity rate 17%	

TABLE II. VAGINAL PREPARATION, TYPE 2. 43 PATIENTS

OPERATIVE RISK, CLASS	NUMBER OF PATIENTS	NUMBER MORBID	PATIENTS MORBID DUE TO PELVIC COMPLICATION
I	7	1	1
II	27	7	7
III	8	4	2
IV	1	0	0
Gross morbidity rate 28%		Net morbidity rate 23%	

In the third group, 2 patients had pulmonary atelectasis, and one had a wound infection. It is noted that patients who are Class IV risks are often afebrile, probably because the surgeon is more meticulous in these cases. The converse holds with Class I patients.

*Sulfamylon is a topical sulfonamide, active in the presence of pus and blood, chemically 4-aminomethylbenzenesulfonamide hydrochloride.

†The penicillin-streptomycin suppositories originally used by us were custom made by the hospital pharmacist, Mr. W. M. Hartmann, and contained 100,000 units of crystalline potassium penicillin G with 250 mg. of dihydrostreptomycin base, in cocoa butter.

TABLE III. VAGINAL PREPARATION, TYPE 3. 44 PATIENTS

OPERATIVE RISK, CLASS	NUMBER OF PATIENTS	NUMBER MORBID	PATIENTS MORBID DUE TO PELVIC COMPLICATION
I	4	2	1
II	25	2	1
III	14	3	3
IV	1	0	0
Gross morbidity rate 16%		Net morbidity rate 11%	

In the group with Type 4 vaginal preparation one patient developed acute enteritis coincidentally with her family on the first postoperative day. Two other patients developed minimal early morbidity not requiring antibiotics, fairly definitely attributable to oozing from areas of severed adhesions.

TABLE IV. VAGINAL PREPARATION, TYPE 4. 40 PATIENTS

OPERATIVE RISK, CLASS	NUMBER OF PATIENTS	NUMBER MORBID	PATIENTS MORBID DUE TO PELVIC COMPLICATION
I	6	2	1
II	21	1	0
III	11	1	0
IV	2	1	1
Gross morbidity rate 12%		Net morbidity rate 5%	

The group that had Type 5 vaginal preparation was not carried beyond 33 patients because in it more frequent and more severe morbidity was encountered than in any other group. The principle to be determined was whether examination of the patient in the hospital by the house staff (usually two members) increased operative risk by disseminating infection from the cervix or other sites into the pelvic lymphatics. This series proved to the satisfaction of the Gynecological Group that examination by the house staff was not deleterious. One patient in the group developed pulmonary atelectasis, another a wound infection.

TABLE V. VAGINAL PREPARATION, TYPE 5. 33 PATIENTS

OPERATIVE RISK, CLASS	NUMBER OF PATIENTS	NUMBER MORBID	PATIENTS MORBID DUE TO PELVIC COMPLICATION
I	11	1	1
II	13	4	3
III	7	3	3
IV	2	1	1
Gross morbidity rate 27%		Net morbidity rate 24%	

As a comparison, 49 consecutive total abdominal hysterectomies performed by general surgeons at this hospital during the same period were analyzed. The surgical risk distribution could not be determined with complete accuracy, but was judged to be similar, from the pathological reports, with 15, 19, 12, and 3 patients in Classes 1, 2, 3, and 4, respectively. The gross morbidity rate in this group was 27 per cent, and the net rate 22 per cent, with 2 wound infections, one deep thrombophlebitis, and one pyelonephritis.

When the results of these studies became apparent, the Group elected to use the penicillin-streptomycin suppository before all contemplated and possible total abdominal hysterectomies. This has been done, and, to date, another series in which this preparation was used is available for comparison, consisting of 40 patients. The gross morbidity rate in this group was 15 per cent, and the net rate 8 per cent. There was one instance of acute bronchitis,

one of cystitis causing a delayed morbidity, and one of paralytic ileus. The risk distribution in this group was 5, 17, 17, and 1 patients in Classes 1, 2, 3, and 4, respectively.

A summary of the results in each of these groups is presented in Table VI.

TABLE VI. SUMMARY OF RESULTS WITH DIFFERENT TYPES OF VAGINAL PREPARATION BEFORE TOTAL ABDOMINAL HYSTERECTOMY. 290 PATIENTS

TYPE OF PREPARATION	NUMBER OF PATIENTS	GROSS RATE OF MORBIDITY (%)	RATE OF PELVIC MORBIDITY (%)
2. Dry tampon	43	28	23
6. Surgeons' cases	49	27	22
5. No preparation	33	27	24
1. Sulfamylon	41	20	17
3. Tincture of Zephiran	80	16	11
4. Suppository	44	14	6

Mortality

There was one death during the period of this study, which occurred 47 hours postoperatively, caused by acute adrenal cortical insufficiency in a patient with Sheehan's syndrome and carcinoma of the endometrium; an autopsy was performed.

Analysis

We have been impressed by the results obtained in this study. The only legitimate objection is that the series may be too small for complete validity. If we consider the group of 80 hysterectomies performed after vaginal preparation with the suppository, however, only 11 of these patients had a morbid course, and, of these, only 5 had morbidity of pelvic origin. This is a gross morbidity of 14 per cent and a net morbidity of 6 per cent. Considering all the other 210 cases as a group, the gross morbidity was 23 per cent and the net morbidity 20 per cent. The difference between the net morbidity rates is statistically significant, while the difference in the gross morbidity is probably significant. In only 7 cases out of 100 would one expect to get such a difference by chance alone.*

Summary

The mortality rate following total abdominal hysterectomy nowadays is usually less than 2 per cent, but the rate of risk to the patient's life and well-being, based on the postoperative morbidity rate, is still rather high, averaging about 35 per cent. It was therefore considered worth while to study methods whereby this rate of risk might be reduced. We have done this by a critical appraisal of the individual patient and of the surgical technique in 290 cases. Our results have been found statistically valid.

*For the entire series of 290 cases, the gross morbidity, $p = \frac{60}{290} = 0.207$,

and the net morbidity is $p^1 = \frac{46}{290} = 0.159$.

Then $n_1 = 80$, $p_1 = \frac{11}{80} = 0.1375$, $n_2 = 210$, $p_2 = 0.2333$.

$\text{Sigma}_{p_2 - p_1} = \sqrt{\frac{pq}{n_1} + \frac{pq}{n_2}} = 5.3$, $\frac{p_2 - p_1}{\text{Sigma } p_2 - p_1} = 1.8$ and $P = 0.07$.

Similarly, $p_1^1 = 0.0625$, $p_2^1 = 0.1952$, and $\frac{p_2^1 - p_1^1}{\text{Sigma } p_2^1 - p_1^1} = 2.8$ and $P = 0.01$.

Conclusions

1. The pelvic morbidity rate following total abdominal hysterectomy is reducible to less than 10 per cent in any consecutive series.

2. Part of the risk of hysterectomy is intrinsic in the patient, due to such factors as obesity, metabolic disease, and the type of pelvic pathology.

3. A greater part of the risk of hysterectomy is extrinsic, depending on surgical technique and pre- and postoperative care.

4. An important part of the preparation for hysterectomy is the vaginal phase. Our best results have been obtained with the use of a penicillin-streptomycin suppository inserted into the posterior fornix of the vagina, twelve to sixteen hours before operation.

5. Simple drying of the vaginal vault is equivalent to no preparation before operation.

6. Sulfamylon and tincture of Zephiran are of some value in preparation of the vaginal vault before hysterectomy.

7. Wound infection is preventable.

Grateful acknowledgment is made to the members of the Gynecological Group of Ellis Hospital; namely, Drs. Phillips, Cornell, Meyerhoff, McGrane, Tischler, Jameson, and Kathan, who cooperated to the fullest in establishing and testing the often tedious routines in the operating room, and of whose patients this series is almost completely composed.

The operating-room staff, likewise, under the direction of Miss Rosa Kennedy, R.N., performed many more than their usual duties so that this work might be accomplished.

The statistical analyses were performed by Miss Elizabeth Parkhurst, Associate Biostatistician in the Bureau of Vital Statistics of the Department of Health, State of New York.

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OVARIAN TUMORS IN CHILDREN

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OVARIAN tumors in children are relatively uncommon. The literature contains periodic references to them, but the number of cases reported by any single observer has been small. I believe the early recognition and surgical treatment are of sufficient importance to report this series of 25 cases observed in children under 14 years of age on the surgical wards of the Hospital for Sick Children from 1923 to 1952, inclusive.

The first report of ovarian tumors in children was a review of the literature up to 1904 made by Wiel.[1] There were 60 cases. In 1921 Downes[2] collected 26 previously unreported cases of ovarian tumors in children under 10 years of age. Loeb and Levy[3] in 1932 reported an additional 35 cases. In 1937 Witzberger and Agerty[4] collected all cases of ovarian tumors in children up to and including 10 years of age, which they could find in the world literature. They numbered 186 cases. Ladd and Gross[5] in their textbook *Abdominal Surgery in Infancy and Childhood* list 25 cases from the Children's Hospital, Boston. The last series reported was in 1949 when Dargeon[6] wrote of 14 cases observed in three New York hospitals. Undoubtedly there have been many other cases reported since the last review in 1937 and it is impossible to say how many cases have been found and not reported.

Clinical Data

Age Distribution.—

The age distribution of the 25 cases of the present series is shown in Table I. Of the 2 cases which occurred under the age of 1 year, one was in a 9-day-old infant, the other in a 5-month-old infant.

Table I. Age Distribution in 25 Cases of Ovarian Tumor in Children

Under 1 year	2	8 years	1
2 years	1	9 years	1
3 years	4	10 years	2
4 years	1	11 years	3
5 years	1	12 years	0
6 years	1	13 years	3
7 years	2	14 years	3

Signs and Symptoms.—

A mass or abdominal enlargement was noted in 12 cases prior to hospital admission. The duration of the presence of the enlargement varied from 22 months to 3 days. It was the only sign in 4 cases. In the hospital the tumor mass was felt preoperatively in 20 cases. It was demonstrated by x-ray alone in 1 case and in 4 cases was not demonstrated prior to surgery.

Abdominal pain was present in 18 cases. The duration of pain has been subdivided as follows: acute (less than 48 hours)—8 cases; subacute (under

1 week)—4 cases; chronic (under 1 year)—6 cases. It is noted that the pain was recurrent in 6 cases. Nausea and vomiting were prominent symptoms in 12 cases.

A prolonged menstrual period of 2 weeks' duration occurred in one of the 2 patients in whom menses had started. X-ray studies showed either an increased density or evidence of pressure on surrounding structures in 5 out of 6 cases studied by this means.

Properative Diagnosis.—

Ovarian tumor was the only diagnosis in 5 cases and was mentioned specifically in a differential diagnosis in another 3 cases. Acute appendicitis with or without mass was the diagnosis in 7 cases, mesenteric cyst, 4 cases, intra-abdominal tumor, 2 cases, megacolon, 1 case, and no definite preoperative diagnosis was made in 3 cases.

Treatment.—

The interval from onset of signs and symptoms to the time of surgery varied from months to a few hours. One is impressed, however, by the delay in treatment in the majority of these cases.

The type of procedure carried out was oophorectomy alone in 13 cases, salpingo-oophorectomy in 11 cases, and biopsy in 1 case. Incidental appendectomy was done in 11 cases.

The right ovary was involved in 17 of the 25 cases. In no case was the tumor bilateral.

Postoperative Course.—

The majority of these patients had an uneventful postoperative course. A progressively downhill course and death occurred in 3 of the patients with malignant tumors while the fourth patient, in whom the tumor was diagnosed as malignant, a granulosa-cell carcinoma, did very well and is alive and well today, 18 years postoperatively.

The other complications were generalized peritonitis due to hemolytic streptococcus, with death in 36 hours, and, in a second case, wound dehiscence on the fifth postoperative day. This patient did well after secondary closure of the abdomen.

An adequate follow-up was obtained in only one-third of the cases. The only complication has been one case of intestinal obstruction three years following the original procedure.

Pathological Diagnosis.—

A. Benign:

1. Follicular cyst
   Simple 3
   Multilocular 2
2. Teratoma 14
   In the original pathological reports there were 6 tumors termed as dermoids.
3. Undetermined 2
   The cyst type in two cases could not be determined due to the large amount of hemorrhage present as a result of torsion, but no doubt they were benign.

B. Malignant:

The original pathological reports and sections in the following 4 cases were reviewed and freshly cut sections examined. There were variations noted from the original descriptions and diagnoses. The more correct findings are as follows:

1. Papillary adenocarcinoma
   The sections show a typical picture of undifferentiated papillary adenocarcinoma composed of large polygonal cells with large hyper-

chromatic vesicular nuclei. In some places they form small or large gland acini. Mitotic figures are quite numerous and the tumor is highly vascular.

2. Dysgerminoma
The section shows a varying picture. In some areas the cells lie in nests separated by thin, fibrous tissue septa, while, in others, the cells lie in cords separated by more abundant fibrous tissue stroma. The cells are large and ovoid shaped with large, round, dark-staining nuclei. The cytoplasm is pale and abundant.
There is moderate lymphocytic infiltration of the fibrous tissue.
3. Sarcoma (mixed-cell type)
The tissue for examination was a biopsy specimen of the tumor and the original sections as well as the recently cut sections show poor cytology. There are present, however, some features of a granulosa-cell carcinoma. Because no definite diagnosis could be made, the original diagnosis has been used.
4. Granulosa-cell carcinoma
There is a varied pattern of growth present. A great part of the section shows broad sheets of oval cells varying in size and shape, and numerous mitotic figures. These cells resemble granulosa cells. In other fields there is the more typical pattern where the cells have arranged themselves about a central cystic space resembling Graafian follicles. These follicles are of varying size. There is no connective tissue overgrowth in the tumor.

Comment

This series is fairly representative of the variety of ovarian tumors most frequently found during childhood. The most common was the benign teratoma, usually cystic, which occurred in 14 cases, or 56 per cent of the total. Cystomas accounted for 5 cases, or 20 per cent, malignant tumors numbered 4, or 16 per cent, and there were 2 cystic tumors, type undetermined because of severe hemorrhage present. Table II shows the common types and proportion of each that have been studied.

TABLE II. TYPES OF TUMOR OCCURRING IN CHILDREN AS REPORTED IN FOUR SERIES OF CASES

PATHOLOGICAL DIAGNOSIS	WITZBERGER AND AGERTY REVIEW	DARGEON SERIES	LADD AND GROSS SERIES	PRESENT SERIES	TOTAL	PER CENT
Simple and multilocular cysts	60	3	4	5	72	28.8
Benign teratoma (including dermoids)	55	5	8	14	82	32.8
Malignant tumors (combined)	70	4	13	4	91	36.4
Miscellaneous	1 heman-gioma	1 fimbrial 1 par-ovarian		2 grossly hemorr-hagic	5	2.0
Total	186	14	25	25	250	100

The term dermoid will be found used in many reports but actually benign teratoma is the correct term. Teratoma may be malignant and the cells undifferentiated, or benign and show well-differentiated cells. The latter type is commonly cystic.

Striking clinical findings may be associated when the tumors are hormone producing. Granulosa-cell tumors may produce precocious puberty with the typical findings of vaginal bleeding, hypertrophy of the breasts, nipples, and labia, uterine enlargement, and increased secretion of estrogen in the urine. There was no clinical evidence of increased estrogen production in the one child in this series with such a tumor. Bland and Goldstein[7] reported 12 cases in children under 14 years in their series of 150 cases of granulosa-cell tumor. In 1941 Lull[8] stated that there were 16 cases of ovarian tumors reported in children who had shown signs of precocious puberty. These tumors show great variability in malignant potential.

There have been no cases of arrhenoblastoma, the masculinizing tumor, reported in children under the age of 15 years. Novak,[9] in a review of 17 cases of dysgerminoma, found 3 in children under 14 years. This tumor exerts no endocrine activity, being composed of sexually indifferent cells. It is often observed, however, in sexually underdeveloped or pseudohermaphroditic individuals. These sex variations remain after removal of the tumor. The child in this series with this tumor presented no abnormal sex variation. Here again there is a wide variation in malignancy in individual cases.

To the clinician there are several important considerations in the management of children with ovarian tumors.

The condition is insidious and is often overlooked as the tumor may become quite large before causing symptoms. Consequently, the case may come under observation either before or after complications have set in. The diagnosis should be considered when one observes lower abdominal pain, acute, subacute, or chronic in nature, abnormal abdominal or pelvic masses, or precocious puberty and vaginal bleeding.

In this series approximately one-half of the cases presented with an abdominal or pelvic mass or abdominal enlargement, with frequent attacks of pain and vomiting. In 6 of these cases the symptoms had subsided only to recur at a later date. Here one should think of a cyst that has twisted and untwisted itself. With the history of pain, vomiting, temperature elevation, with signs of peritoneal irritation, one of course must include ovarian tumor in the differential diagnosis along with appendicitis, appendiceal abscess, intussusception, urolithiasis, and incomplete bowel obstruction.

When one finds a tumor mass, the condition will have to be considered along with kidney tumor, distended bladder, cysts of the urachus, mesentery or liver, hematocolpos, hematometra, hematosalpinx, pregnancy, metastatic growths and ascites.

The physical findings are dependent on the size of the tumor and the presence or absence of complications. If sufficiently large to be felt on abdominal examination it is palpable usually as a firm, tender, mobile mass. The most valuable aid in diagnosis probably is a bimanual examination since the pelvis can usually be completely explored in these young girls. Acute symptoms of course will result from torsion of the pedicle. This was present in 9 cases in this series and was mistaken for appendicitis in 6 of these cases.

X-rays of the abdomen are of definite aid since the possibility of stones in the urinary tract can be excluded and definite soft tissue shadows may be seen in the pelvis or evidence of pressure on surrounding structures. Increased densities due to calcium deposits in the teratomas will be evident.

The leukocyte and differential counts are extremely variable.

The technical problem of removing these tumors is not difficult and the postoperative complications have been few. It has been recommended that the pedicle be clamped proximal to the twisting before manipulation in order to prevent possible emboli.

Summary

1. Data from 25 cases of ovarian tumors in children under 14 years of age have been discussed.

2. While not a common finding in intra-abdominal pathology, the diagnosis is not difficult if one considers the possibility of the condition in infants and children of any age.

3. Abdominal pain, with or without vomiting, and an abdominal or pelvic mass are the common findings.

4. The tumors are potentially dangerous to the patient. Therefore the treatment should be prompt surgical removal. In the case of malignant tumors where complete surgical removal is not feasible, postoperative deep x-ray radiation should be given.

5. The prognosis in the benign type is good, in the malignant varieties it is usually serious.

I wish to thank Dr. William Anderson and Dr. J. Fisher for their invaluable aid in the review of the pathological sections.

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OVARIAN DYSGERMINOMA WITH CHORIONEPITHELIOMA*

Report of a Case

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OVARIAN dysgerminoma with chorionepithelioma is a malignant tumor. This tumor elaborates a gonadotropic hormone, producing precocious sexual development, when it occurs before puberty.

There have been very few cases of the combined tumors reported in the literature and no single case reported in detail in which hormonal assays have been carried out. A limited number of primary chorionepitheliomas of the ovary with evidence of precocious sexual development have been collected. A small number of cases of ovarian dysgerminoma with a positive Aschheim-Zondek test and associated precocious puberty have also been recorded. The finding of evidence of sexual precocity and positive Aschheim-Zondek test in both these tumors, as well as their reported association in one ovary, has given rise to a great deal of speculation concerning the histogenesis.

The case to be reported was included in an analysis of 17 cases of dysgerminoma of the ovary reported by Pedowitz and Grayzel,[5] but it has never been described in detail.

Case Report

A. M., No. 331278, an Italian white girl, 13 years of age, was admitted to the Jewish Hospital of Brooklyn on Sept. 29, 1949, on the private service of the author, with the chief complaint of lower abdominal pain of one month's duration. The girl was mentally retarded.

A history was obtained from the mother to the effect that she first complained of abdominal pain one month prior to admission. The pain lasted for one week and, at one time, was severe enough to cause the patient to cry out and vomit. The pain diminished in intensity and finally left completely. Two weeks prior to admission, the patient again complained of vague lower abdominal pain, not related to food or bowel habit. At that time her mother noted a mass in the abdomen.

Menses had begun at 12 years of age, occurred regularly each month, and lasted five days. The last menstrual period occurred one month prior to admission.

Examination showed the child to be well developed for her age, with secondary sex characteristics and slight acne of the face. There was moderately excessive hair growth on the extremities and upper lip. The breasts were large and overdeveloped for that age (Fig. 1). Abdominal examination revealed the presence of a smooth, firm mass, filling the entire lower abdomen, arising from the pelvis and extending to the umbilicus. Examination of the external genitals revealed a normal clitoris. On rectal examination, the cervix was posterior and the uterus anterior, retrocessed, and small. The mass felt abdominally apparently arose from the right adnexal region.

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The clinical impression recorded on admission was of a solid ovarian tumor, possibly teratoma or embryonal-cell carcinoma or dysgerminoma.

Blood studies revealed a hemoglobin of 51 per cent, 8,500 white blood cells with 63 per cent polymorphonuclear leukocytes, 2 per cent band cells, 4 per cent eosinophils, and 31 per cent lymphocytes. Blood chemistry revealed nothing significant. The blood Wassermann test was negative.

An Aschheim-Zondek test taken on admission was recorded as positive. Another urine specimen was obtained for an Aschheim-Zondek test in dilution. This was reported as positive in dilution of 1:100 and negative in dilutions of 1:200 and 1:500. Quantitative hormone studies showed urinary gonadotropin positive with 40,000 mouse units, estrin positive with 9⅛ rat units, and the 17-ketosteroid excretion, 7.2 mg. for 24 hours. A flat plate of the abdomen revealed a soft tumor springing from the pelvis, but no evidence of fetal parts. A rather pronounced opacity was demonstrated springing from the pelvis which had to be looked upon as a soft tissue tumefaction, possibly an ovarian tumor or retroperitoneal growth.

X-ray of the chest on Oct. 5, 1949, revealed the lung fields to be clear. X-ray of the skull on Oct. 7, 1949, showed the anteroposterior diameter of the sella turcica somewhat narrowed superiorly, but otherwise the sella was well formed. There was no atrophy or erosion of the clinoids or the floor.

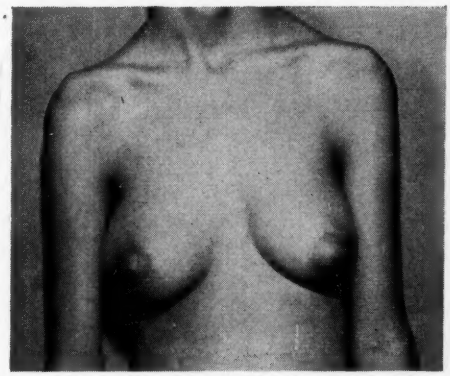

Fig. 1.—Girl, 13 years of age, with marked hypertrophy of breasts.

During the first week's hospital stay, the patient had several episodes of severe lower abdominal pain with temperature ranging up to 101° F. On the seventh hospital day, she had a rather severe attack of lower abdominal pain, predominantly in the right lower quadrant. On examination, there was marked tenderness of the right lower quadrant and, on palpation of the mass, the impression was one of hemorrhage or necrosis of the ovarian tumor.

On Oct. 12, 1949, a laparotomy was performed under general anesthesia through a lower midline incision. The right ovary was found to be replaced by a solid gray-white tumor mass measuring approximately 8 by 6 by 4 inches with hemorrhagic areas on the surface and one area of perforation at the upper pole with the omentum wrapped around it at the site of perforation. There were metastatic nodules about the size of a marble in the omentum, four in number. The left ovary was slightly larger than normal, approximately the size of an egg and gray white. Both tubes were slightly congested but otherwise normal. The uterus was hypoplastic, smooth, and with normal configuration. The liver was palpated. It was smooth and no metastatic nodules were felt. No aortic or common iliac or external iliac nodes were palpated. A total hysterectomy and bilateral salpingo-oophorectomy were performed with resection of the metastatic nodules in the omentum. The postoperative course was uneventful. The temperature rose to 102° F. on the first postoperative day, subsided to 101° on the second day, and was normal on the third day and remained so until discharge. The wound was healed by primary union.

A repeat Aschheim-Zondek test on October 20, the eighth postoperative day, was negative. An Aschheim-Zondek test done on October 24 was also reported as negative. To complete the hormonal investigation, a large portion of the ovarian tumor was ground up and extracted with water and analyzed by the usual methods in the endocrine laboratory. The presence of gonadotropic hormone was not demonstrated in the extract of the tumor. Prior to discharge, x-ray of the chest showed no evidence of metastatic disease and the skeletal structures of the upper and lower extremities were radiographically normal. The patient was discharged on October 25, the thirteenth postoperative day.

One week after discharge, x-ray therapy was started and given daily to the lower abdomen anteriorly and posteriorly. Because of the increasingly severe abdominal pain, however, the patient was admitted to the Brooklyn Cancer Institute on Nov. 12, 1949, for continuation of the postoperative radiation therapy. She was too sick to be given immediate therapy. The temperature ranged up to 102° F. and the abdomen was slightly distended and tense. Supportive therapy was instituted, including antibiotics, blood transfusions, and parenteral fluids. X-ray examination of the chest showed the diaphragm to be high, and the presence of a 3 by 1½ cm. area of consolidation in the right lower lung field. There was no evidence of pneumonia or pleural effusion. The area noted was considered to be a metastatic focus.

Fig. 2.—Cut surface of right ovarian dysgerminoma with chorionepithelioma, with rent in capsule at lateral pole, showing, in medial half, homogeneous tumor divided into lobules by septa, and, in lateral half, four red-brown circumscribed areas of chorionepithelioma.

In spite of all therapy the patient died on Nov. 24, 1949, twelve days after admission. Permission for autopsy was not granted.

The report of the pathologist was as follows:

Gross Pathology.—(S. P. 49-4789.) The uterus measured 6.5 by 4.5 by 2 cm. and was of the usual shape. The endometrium was thin and smooth throughout. The left ovary measured 4 by 3 by 1.5 cm. Its outer surface was smooth. On section, approximately six thin-walled, smoothly lined cysts up to 0.5 cm. in diameter were noted within the interior. Several cysts contained hemorrhagic fluid and several contained watery, amber fluid.

The right ovarian mass was firm, roughly ovoid in shape, and measured 18 by 14 by 8.5 cm. It was completely invested by a thin, smooth, yellow-gray capsule, except at the lateral pole where a rent in the capsule exposed soft, red-brown hemorrhagic tissue. The cut surfaces of the tumor were homogeneous, pale yellow brown, and divided into lobules by delicate, narrow septa. In the lateral half of the tumor, four roughly round, circumscribed areas composed of slightly elevated, spongy, soft red-brown and gray tissue were noted. These measured up to 4 cm. in diameter. Part of one such mass was exposed by the rent in the capsule (Fig. 2).

Microscopic Pathology.—

Uterus: The endometrium was composed of slightly tortuous, nonsecretory glands rather widely separated by much stroma. Stromal cells were small and did not appear to be of decidual type. The myometrium was not unusual.

Right ovarian mass: (Fig. 3.) Sections from the medial half showed the presence of solid nests and cords of polygonal or round cells with little cytoplasm and relatively large, round hyperchromatic nuclei. Fibrous septa were very conspicuous and divided the tumor into alveoli containing the nests and cords of cells. The septa were sprinkled with lymphocytes. An occasional multinucleated giant cell with eosinophilic cytoplasm and small, round peripheral nuclei was also present. Sections through the spongy masses showed them to consist chiefly of blood, acellular eosinophilic material and, at the periphery, of bands and nests of very large cells divisible broadly into two types (Figs. 4 and 5): (1) a large, round or irregularly polygonal cell with large vesicular nuclei, granular or clear cytoplasm, and distinct cytoplasmic borders; and (2) an elongated cell with eosinophilic cytoplasm and intensely hyperchromatic, irregular nuclei. These types correspond to Langhans and syncytial cells. Such areas were generally separated from the smaller cells seen in the medial half of the tumor by narrow, fibrous septa. There was no indication of a gradual transition between the two types of tumor.

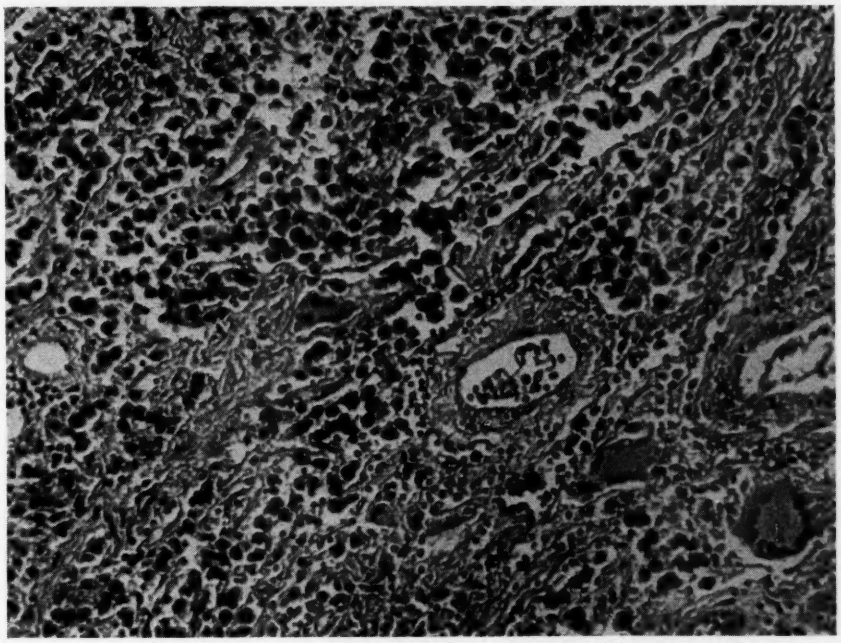

Fig. 3.—High-power photomicrograph of medial half of ovarian tumor, showing dysgerminoma cells in sheets and columns separated by fibrous septa containing lymphocytes. A multinucleated giant cell is seen in lower right-hand corner. (×300; reduced ¼.)

Left ovary: One degenerating corpus luteum of small size was noted. The cysts were generally lined by granulosa cells. In some, the theca interna layer was prominent and the cells moderately enlarged.

Omental masses: These consisted of areas of hemorrhage and nests of cells composed of an admixture of Langhans and syncytium-like elements. No areas corresponding to the dysgerminomatous component are seen (Fig. 6).

Diagnosis: (1) right ovary with dysgerminoma containing foci of chorionepithelioma, (2) metastatic chorionepithelioma in omentum, (3) left ovary with follicular cysts.

Comment

Very few cases of dysgerminoma with chorionepithelioma, similar to the one described, have been reported in the literature. In 1950, Mueller, Topkins, and Lapp[1] reviewed 427 cases of dysgerminoma in the literature and reported only 3 associated with teratoma, one with granulosa tumor, and none with

Fig. 4.

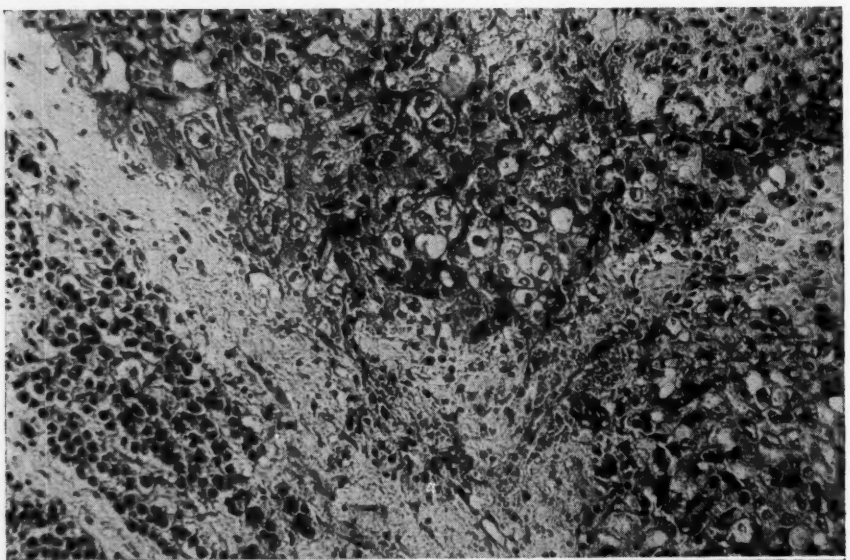

Fig. 5.

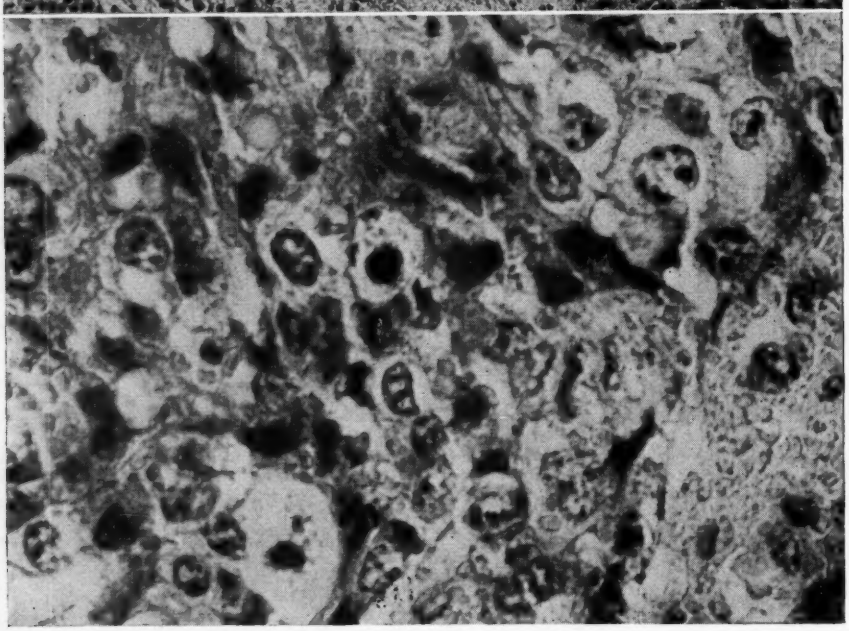

Fig. 4.—High-power photomicrograph of ovarian tumor, showing dysgerminoma cells to the left separated from chorionepithelioma by fibrous septum. (×300; reduced ¼.)

Fig. 5.—Higher-power photomicrograph of chorionepithelioma cells, showing bizarre nuclei of syncytial cells and vesicular nuclei of Langhans cells. (×600; reduced ¼.)

chorionepithelioma. Ewing,[2] in his textbook, stated that he observed one case in which dysgerminoma was associated with teratoma and chorioma. In 1947, Santesson,[21] reviewing ovarian dysgerminomas treated at the Radiumhemmet, reported 4 tumors "in which are found different combinations of both adenopapilliferous, choriomatous, teratoid and dysgerminomatous structures." He did not describe these cases, however, or indicate how many were a combination of chorionepithelioma and dysgerminoma. Marrubini,[3] in 1949, reported 2 cases of primary ovarian chorionepithelioma. In one of the 2 ovarian tumors, he described "part of the ovarian tissue bearing a close resemblance to the structure of dysgerminoma."

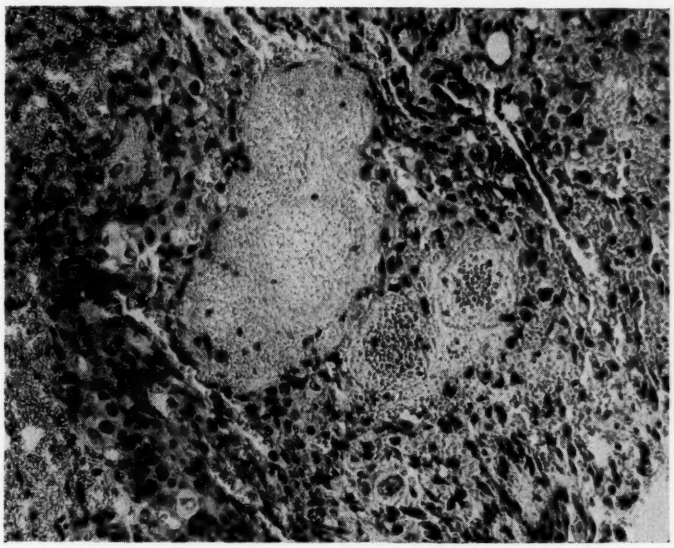

Fig. 6.—High-power photomicrograph of omental metastasis, showing chorionepithelioma with syncytial cells, omental fat, hemorrhage, and distended blood. (×300; reduced ¼.)

Black-Schaeffer and Kambe[4] reported an ovarian dysgerminoma which metastasized to the omental lymph nodes. The latter grossly were hemorrhagic and microscopically revealed a characteristic choriocarcinoma with prominent syncytial trophoblastic cells. They did not report the presence of choriocarcinoma in the ovary.

Another case of dysgerminoma was recently reported,[5] in which "chorionepithelioma was found in the metastases shortly after the primary operation, despite the fact that no such tumor was found in the ovary."

In 1904 Pick[6] first described a pure chorionepithelioma of the ovary associated with a teratoma in a 9-year-old girl. In 1948, Oliver and Horne[7] reviewed the world literature and reported 13 additional proved cases, including their own case report with positive Aschheim-Zondek test. They eliminated all other reported cases which followed pregnancies because they "may have represented metastases from uterine chorionepithelioma that regressed spontaneously, were expelled with the placenta or were removed by the curette." They felt that "a primary ovarian chorionepithelioma can be assumed with

certainty only in a child." Nine of the 14 cases reported occurred in children before the age of puberty, 5 of whom presented evidence of precocious sexual development or vaginal bleeding.

The following year, Marrubini[3] reviewed the world literature and found 18 cases of primary ovarian chorionepithelioma and added two new cases. Roman, Vincent, and Feroldi,[8] and Jauch[9] also recently reported single cases of primary chorionepithelioma of the ovary.

A small number of cases of pure ovarian dysgerminoma with positive Aschheim-Zondek test and associated precocious puberty, or menstrual irregularity in the sexually mature woman, have been reported. Hain[11] described an 8-year-old girl with excessive breast development, vaginal bleeding, and strongly positive Aschheim-Zondek reaction, with regression of all signs of precocity following removal of an ovarian dysgerminoma. He also reported 5 other recorded cases up to that time in which dysgerminomas were associated with an excessive secretion of chorionic gonadotropin and two cases "in which demonstrable hormone secretion may be inferred, since precocious puberty accompanied the tumor," but in neither of which were hormone investigations carried out. In all cases, there was an absence of teratomatous or chorionic elements. Burge[10] described 2 cases with strongly positive Aschheim-Zondek test in 23-year-old single women. Moreton and Desjardins,[19] reviewing 11 cases of dysgerminoma, reported one with a positive Aschheim-Zondek test. Schomaker and associates[20] also reported one case of dysgerminoma with a positive Friedman reaction.

Geist[12] stated in his textbook that "Salmon has isolated a gonadotropic hormone from a dysgerminoma." This has not been confirmed by any report in the literature.

Thus, apparently, the primary chorionepithelioma of the ovary elaborates a gonadotropic hormone, as well as the dysgerminoma with associated chorionepithelioma and, possibly, the dysgerminoma.

The incidence of pure dysgerminoma with evidence of gonadotropic hormone production, in the total number of reported dysgerminomas, is extremely low, however, namely, only 6 reported cases of precocious puberty with positive Aschheim-Zondek test, 2 cases with precocious puberty in which Aschheim-Zondek tests were not done, and only a small number of positive Aschheim-Zondek tests in the sexually mature women with pure ovarian dysgerminomas. The latter is not significant because Aschheim-Zondek tests are not frequently done prior to laparotomy. Since there is no evidence that the dysgerminoma cell is capable of producing gonadotropic hormone, we must look for other sources of hormone production. Is it possible that the latter may be due to an increase in pituitary gonadotropin resulting from the replacement of ovarian tissue by tumor and causing an oversecretion of tropic hormones by the pituitary? Precocious mammary hypertrophy and positive Aschheim-Zondek tests have been reported in girls with simple granulosa or theca lutein cysts of the ovary.[17] Or is it likely that foci of chorionepithelioma have been overlooked in the pure dysgerminoma because of inadequate sampling and the gonadotropin is chorionic in origin?

Hain, in commenting on his reported case of pure dysgerminoma with sexual precocity, stated "that it is unnecessary to assume that elements other than those of the dysgerminoma gave rise to the secretory activity which caused the pregnancy test to be positive because testicular seminomas are often associated with excessive secretion of follicle stimulating hormone. If the testicular counterpart of the ovarian 'false seminoma' can be highly secretory, why should not the ovarian tumor have marked hormonal effects in some cases?" However, Dixon and Moore[18] reported that "in 14 per cent of pure seminomas syncytial trophoblastic cells were present, which corresponds almost exactly to the proportion of patients found to have elevated urinary gonadotropin."

There has been a great deal of discussion concerning the histogenesis of the tumor. Is the association simply coincidental or do the tumors arise from a single parent cell?

The dysgerminoma is generally believed to be hormonally indifferent. This conforms with Robert Meyer's[13] concept of its origin from "an undifferentiated form of germinal cells which have lost their faculty of becoming either masculine or feminine in type."

Ewing,[2] Teilum,[14] Wolfe and Kaminester,[15] and, recently, Friedman and Moore,[16] and Pedowitz and Grayzel[5] have suggested a totipotent cellular origin from a cell belonging to the sex cell series.

Histologically, the dysgerminoma is identical with the seminoma of the testis. Friedman and Moore reported on 922 cases of tumors of the testis, of which 35 per cent were seminomas, 19 per cent embryonal carcinomas, 35 per cent teratocarcinomas, 7 per cent teratomas, and 0.4 per cent pure chorionepitheliomas. In about 4 per cent of the tumors, however, both seminomatous and embryonal carcinomatous tissues were encountered and foci of chorionepithelioma were encountered in about 6 per cent of embryonal carcinoma. They considered the chorionepitheliomas as a subvariety of the embryonal carcinomas. Furthermore, they frequently found choriomatous characteristics in the metastases of embryonal carcinomas even when they were not manifest in the primary tumor. They concluded that "seminomas are probably tumors of primordial germ cells" and "embryonal carcinomas and teratoid tumors are neoplastic expressions of the unlimited potencies of embryonic cells."

Similarly, the association of dysgerminoma with chorionepithelioma, the reported occurrence of chorionepithelioma in the metastases of pure dysgerminomas, and not infrequent occurence of other mixed tumors of the ovary would suggest a single-cell origin for these ovarian tumors and development along lines suggested by Friedman and Moore for testicular tumors.

If the direction of development of the totipotent cell of the primitive gonadal mesenchyme is along feminine lines, a feminizing mesenchymoma, either granulosa cell or thecoma, results. If it is along masculine lines, an arrhenoblastoma develops. If the differentiation is both masculine and feminine, a gynandroblastoma is produced. If the direction is neuter, the dysgerminoma results. If the totipotent cell develops as a teratoma, the latter may produce any of the above tumors or a chorionepithelioma.

The pathologic features of this tumor have been described in detail in the case report.

Clinically, ovarian dysgerminoma with chorionepithelioma presents symptoms characteristic of any ovarian tumor plus those due to the presence of excessive gonadotrophic hormone. The symptoms are vague abdominal pain and enlargement and those dependent upon the occurrence of torsion, perforation of the capsule, and the mechanical effects on surrounding viscera. Although dysgerminoma can occur at any age, it is interesting that in all reported cases of dysgerminoma with a positive Aschheim-Zondek reaction, the age varied from 14 to 23 years. In the reported cases of primary chorionepithelioma of the ovary, the age incidence varied from 6 to 27 years, with the majority occurring in the 6 to 14 year age group.

Before puberty, vaginal bleeding or accelerated secondary sex characteristics may occur. After puberty, menstrual irregularities, in the presence of excessive gonadotropic hormone secretion, usually occur.

The Aschheim-Zondek test is of great value. A strongly positive reaction in a young girl with a solid ovarian tumor is highly suggestive and laparotomy is indicated, although, even after laparotomy, the diagnosis is frequently not made until the histological examination is completed.

The outcome in dysgerminoma with associated chorionepithelioma or in primary chorionepithelioma is usually fatal, since the clinical diagnosis is not made until late in the course of the disease. Death occurred in all recorded cases in less than one year. Early diagnosis and adequate surgery before the tumor has spread may improve our results.

The therapy is complete removal of the uterus and adnexa, if the diagnosis is established. In this case there was gross evidence of metastases, indicating the radical procedure.

If a laparotomy is performed on a young girl with a positive Aschheim-Zondek test and a unilateral solid ovarian tumor, with an intact capsule and no gross evidence of spread of the tumor, and the diagnosis of dysgerminoma is established, radical surgery is indicated, in view of the proved high degree of malignancy of even pure dysgerminomas in this age group with positive Aschheim-Zondek tests.

Postoperative x-ray therapy is usually advised, although the value has not been established.

If a conservative procedure has been done at the original operation, either secondary laparotomy is performed or x-ray therapy administered.

Summary and Conclusions

1. A case of ovarian dysgerminoma with chorionepithelioma and chorionepitheliomatous omental metastases in a 13-year-old girl has been described.

2. The symptoms were those of an ovarian tumor with perforation. Precocious breast development was prominent.

3. Preoperative hormone assay revealed a marked increase in the urinary gonadotropin and a strongly positive Aschheim-Zondek reaction, which became negative after operation.

4. The prognosis is grave. This case terminated fatally, despite radical operation and beginning x-ray therapy.

5. The pathologic features of the tumor have been presented. Grossly, the chorionepitheliomatous element was strikingly hemorrhagic. Microscopically, the cells of the dysgerminoma and the Langhans and syncytial cells were distinctive.

6. The literature has been briefly reviewed, including cases of the combined tumor, of primary ovarian chorionepithelioma and pure ovarian dysgerminoma with excessive gonadotropic hormone secretion.

7. The histogenesis of the tumor has been discussed and its origin from a totipotent cell belonging to the sex cell series has been emphasized.

I wish to thank Dr. A. Mackles, Department of Pathology, Jewish Hospital of Brooklyn, for his description of the pathologic material, and Dr. S. A. Wolfe for his constructive criticism.

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THE PRESENCE OF NEISSERIA GONORRHOEAE AND PLEURO-PNEUMONIA-LIKE ORGANISMS IN THE CERVIX UTERI*

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RECENT investigators have reported a high incidence of pleuropneumonia-like organisms (PPLO) in women with gonorrhea, leukorrhea, or other lower genital tract pathology. The significance of the occurrence of PPLO in these conditions is not clear from the data currently available.

The present study has investigated the possible relationship of the presence of PPLO to (1) the gonococcus, (2) leukorrhea, (3) gross genital pathology, (4) various phases of the menstrual cycle, (5) previous penicillin therapy, and (6) the technique of procuring bacteriologic specimens.

Materials and Methods

The data were obtained from a study of 86 Negro women named as sexual contacts by men with evidence of gonorrhea. At weekly intervals, specimens for bacteriologic culture were secured by two methods after exposing the cervix with a speculum: (1) mucus from the cervical os was collected on a sterile cotton swab, and (2) after abrasion of the region of the external cervical os with the splintered ends of several wooden applicator sticks, a second swab was applied to the slightly bloody area. Each swab was immediately placed in 1.5 ml. of a solution at pH 7.2, consisting of 2 per cent proteose peptone No. 3, 0.5 per cent sodium chloride, and 1 per cent soluble starch. One drop of the suspension from each specimen was spread over the surface of the appropriate medium.

Bacto GC medium base with 1 per cent Bacto-hemoglobin and 1 per cent Bacto-supplement B was used for cultivation of the gonococcus. The cultures were incubated at 37° C. for 48 hours in the presence of 10 per cent carbon dioxide. The oxidase test was then employed for the identification of Neisseria. Further identification of Neisseria was obtained by subculture in media consisting of Bacto-phenol red agar base with 0.5 per cent of the appropriate carbohydrate, and enriched with 20 per cent ascitic fluid.

During an earlier study[8] separate cultures were made from the cervix, vagina, and urethra of each of over 500 young women apprehended on morals charges. The gonococcus was detected in one or more specimens of 131 sets of cultures. In 95.4 per cent of the infected individuals, the cervical specimens were positive for the gonococcus. The vaginal and urethral specimens

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each contributed only 2 per cent positive cultures. It therefore seemed satisfactory to culture only the cervix for the diagnosis of gonorrhea.

For PPLO studies, Bacto-PPLO agar, or a freshly prepared beef heart infusion, was enriched with 1 per cent PPLO-serum fraction A. Thallium acetate in a final concentration of 1:1,000 was sometimes added to the medium to aid in the isolation of PPLO.[10] The cultures were incubated aerobically at 37° C. for 5 days. Examinations for PPLO colonies were made with the low power of the microscope. Colonies were identified by their morphology, the inability to remove them with an inoculating needle, and, in doubtful cases, by staining according to the method of Dienes. To ascertain if the PPLO were stable forms, or would change to a bacterial type of growth, 4 of the many strains isolated were transferred to broth medium in the following manner. Agar blocks containing numerous PPLO colonies were placed into beef-heart infusion broth and also into thioglycollate medium, each enriched with 1 per cent PPLO-serum fraction A. After five days' incubation, approximately 0.05 ml. from each culture in infusion broth and in thioglycollate medium was transferred to solid medium (the same as was used for the isolation of the PPLO). The identification techniques previously described for PPLO were then applied. The thioglycollate cultures were again tested in the same manner for the presence of bacterial growth after a further incubation period of 2 months.

Each time cultures were obtained a gynecologic history was taken and a pelvic examination performed.

Results

1. Relationship of PPLO to the Gonococcus (Table I).—The gonococcus (this includes 11 strains of Neisseria which did not survive until fermentation studies were completed) was isolated from 41, or 47 per cent, of the 86 women studied. PPLO were found in 52, or 60 per cent, of the 86. From the 41 patients with gonorrhea, PPLO were isolated from 33, or 80 per cent. In the 45 individuals in whom the gonococcus could not be demonstrated, however, PPLO were identified in only 19, or 42 per cent. This difference is highly significant on the basis of the Chi square analysis[16] (probability of these results being so divergent due to chance alone is less than 1 in 1,000). Therefore, in this population, PPLO were associated with the presence of the gonococcus.

No bacterial type of growth was observed at the end of two months in the cultures of the 4 strains of PPLO tested.

TABLE I. CORRELATION OF THE PRESENCE OF THE GONOCOCCUS WITH PPLO

PPLO	PATIENTS		
	TOTAL NUMBER	NEISSERIA GONORRHOEAE	
		PRESENT*	ABSENT
Present	52	33	19
Absent	34	8	26
Total	86	41	45

$\chi^2 = 12.5$ $p < 0.001$

*Includes some Neisseria which did not survive until species were identified, but which probably were *N. gonorrhoeae.*

2. Leukorrhea (Table II).—The presence of leukorrhea was determined by the examiner, since the questioning of the patient as to the presence or absence of vaginal discharge was found to be unreliable. From 47 women without gonorrhea, specimens were obtained on at least 3 occasions from each of 34

individuals. Seventeen of these 47 women had a noticeable discharge. PPLO were identified in only 6 of the 17 (35 per cent). In 30 women without discharge, PPLO could be demonstrated in 13 (43 per cent). The severity of the discharge could not be correlated with the incidence of specimens positive for PPLO. From these data, there does not appear to be any direct relationship between vaginal discharge and the presence of PPLO.

In the group of 39 women with gonococcal infection, specimens were cultured on at least 3 occasions from each of 33. As shown in Table II, there was a greater frequency of PPLO in women with vaginal discharge and gonorrhea. The association between the presence of PPLO and the gonococcus (Table I), however, is statistically significant, while the relationship of the presence of PPLO to vaginal discharge (Table II) is not.

TABLE II. THE RELATIONSHIP BETWEEN THE PRESENCE OF PPLO AND LEUKORRHEA IN WOMEN WITH AND WITHOUT GONORRHEA

	WOMEN WITHOUT GONORRHEA		WOMEN WITH GONORRHEA	
	LEUKORRHEA		LEUKORRHEA	
PPLO	PRESENT	ABSENT	PRESENT	ABSENT
Present	6 (35%)	13 (43%)	18 (95%)	15 (75%)
Absent	11	17	1	5
Total	17	30	19	20

3. Lower Genital Tract Pathology.—Forty-nine of the 86 patients had gross evidence of lower genital tract pathology. PPLO were isolated from 59 per cent of those with pathology. PPLO were found in 73 per cent of the individuals with no gross pathology. There does not appear to be a correlation between the presence of PPLO and gross pathology of the lower genital tract.

4. Menstrual Cycle (Table III).—When possible, the time elapsed between the previous menstruation and the securing of the specimen was estimated. The cultures positive for PPLO were grouped according to the days of the menstrual cycle. There is no correlation between the isolation of PPLO and a particular portion of the menstrual cycle.

TABLE III. ISOLATION OF PPLO DURING THE MENSTRUAL CYCLE

	ESTIMATED DAYS OF MENSTRUAL CYCLE				
CULTURES	1-4 (menses)	5-10	11-16	17-22	23-28
Number	10	35	37	36	35
Number positive for PPLO	6	21	24	26	21
Per cent positive for PPLO	60	60	65	72	60

5. Previous Penicillin Therapy (Table IV).—Twenty-five patients gave a history of treatment with penicillin within the preceding 12 months. PPLO were isolated from 14, or 56 per cent. In the group of 61 individuals who gave a history of no previous penicillin therapy, 38, or 62 per cent, were positive for PPLO. There is no significant difference in the incidence of PPLO in the group of patients who had had penicillin therapy compared with those who had not.

6. Technique of Procuring Bacteriologic Specimens (Table V).—The results of cultures obtained from the cervical mucus were compared with the results of those obtained from the abraded cervix of the same individuals. When the cultures were positive for either PPLO or gonococci, the organisms could usually be isolated from both the cervical mucus and the abraded cervix. There were instances, however, in which the organisms were present in only one of the specimens. Generally the two techniques gave equivalent results.

TABLE IV. EFFECT OF PREVIOUS PENICILLIN THERAPY ON THE PRESENCE OF PPLO

PATIENTS	PREVIOUS PENICILLIN THERAPY	
	YES	NO
Total number	25	61
With PPLO alone	4	15
With PPLO and gonococci	10	23
Total with PPLO	14 (56%)	38 (62%)

TABLE V. COMPARISON OF RESULTS OF CULTURING MATERIAL FROM THE CERVICAL MUCUS AND ABRADED CERVIX OF THE SAME INDIVIDUALS

ORGANISM	TOTAL NUMBER OF PAIRED CULTURES, ONE OR BOTH POSITIVE	PER CENT OF PAIRED CULTURES		
		CERVICAL MUCUS AND ABRADED CERVIX POSITIVE	ONLY CERVICAL MUCUS POSITIVE	ONLY ABRADED CERVIX POSITIVE
N. gonorrhoeae	64	78	13	9
PPLO	94	78	15	7

Comment

There are several possible explanations for the statistically significant association of PPLO with the gonococcus. This coexistence may be due to (1) the highly selected group of patients, (2) venereal transmission, or (3) the PPLO acting as opportunists in pathologic conditions.

The finding by Nicol and Edward[12] that 34, or 81 per cent, of the women with gonorrhea also harbored PPLO in the vagina is comparable to the incidence of 80 per cent in our series. These workers also isolated PPLO from the rectum in 4 cases. Other workers[6, 12, 13, 15] frequently found the two organisms to coexist. This suggests that the association is common.

The possibility of venereal transmission of PPLO cannot be eliminated. While there are instances of PPLO having been isolated from both husband and wife,[2, 9, 14] the organisms have been isolated also from virgins.[3]

Randall, Stein, and Ayres[13] in a study of 300 consecutive gynecologic patients drew attention to the high frequency with which PPLO could be found in women with leukorrhea. In their work, the incidence of PPLO appeared to be related to the severity of the vaginal discharge. Ruiter and Wentholt,[14] dealing largely with women with nonspecific cervicitis and vaginitis, reported isolation of PPLO from 10 of 14 suffering from leukorrhea. Of 146 women with abnormal vaginal discharge, Freundt[3] found PPLO in 69.2 per cent compared with 29.1 per cent in 175 subjects without leukorrhea.

Our limited data obtained from women who had negative cultures for the gonococcus do not support the finding of a direct association of PPLO with leukorrhea. The fact that over one-half of the individuals in this study had evidence of lower genital tract gross pathology may be an explanation. The present data, however, have not demonstrated any real relationship between the existence of PPLO and gross pathology of the lower genital tract. Apparently, there are no gross pathologic findings which indicate the presence of PPLO.

Melen and Odeblad[7] pointed out a statistically significant difference in the incidence of PPLO between women with inflammatory pelvic disease and those with noninflammatory pelvic disease. Essentially similar findings were reported by other investigators.[3, 12, 13] Freundt[3] indicated that, thus far, exact conditions associated with the presence of PPLO have not been determined.

Since patients with gonorrhea usually have definite microscopic evidence of pathology, they too might be included in the group showing pathology. It should be emphasized that in this study patients from whom the gonococcus was isolated were considered to have genital pathology only where tissue changes were visible grossly. If all cases with positive cultures for the gonococcus were considered to have pathology, there would be a high correlation between genital tract pathology and the presence of PPLO.

Previous penicillin therapy appeared to have no effect on the incidence of PPLO. However, Guilbeau and associates,[5] from the results of culturing the postpartum uterus, reported previous penicillin therapy to be associated with a high incidence of PPLO. The time between treatment and culture for the organisms may be a factor in the results obtained.

The present data support the suggestion of Dienes and Smith[2] and Nicol and Edward[12] that PPLO can act as commensals or opportunists. Since Dienes[1] reported the formation of L type growth forms (organisms with some characteristics similar to PPLO) in gonococcal cultures, others have described transformation of L type colonies into normal bacteria. Moustardier and coworkers[11] suggested the possibility that L organisms isolated from the urogenital tract, which will not revert to bacterial type colonies, may be stable forms of the gonococcus. Thus, the correlation of the coexistence of PPLO with the gonococcus may be significant.

The PPLO have taken on added significance with the finding by Freundt[4] that at least one strain of PPLO isolated from the genitourinary tract of man was identical serologically and similar biochemically and morphologically to the causative agent of bovine pleuropneumonia.

Summary

Eighty-six women named as sexual contacts by men with gonorrhea were studied for the presence of gonococci and pleuropneumonia-like organisms (PPLO). A statistically significant relationship between the presence of PPLO and the gonococcus was found. PPLO were isolated from 80 per cent of the 41 patients with gonorrhea. They were isolated in only 42 per cent of the 45 individuals in whom the gonococcus could not be detected.

The isolation of PPLO from this group of women did not appear to be directly associated with (1) leukorrhea, (2) gross genital pathology, (3) phase of the menstrual cycle, (4) previous penicillin therapy, and (5) culturing material from the abraded cervix, rather than from cervical mucus.

The role of PPLO as opportunists or commensals, and the possibility of these organisms representing a stable form of the gonococcus are discussed.

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TRILENE IN OFFICE GYNECOLOGY*

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THERE are many procedures in gynecology which are not serious enough to warrant hospitalization but necessitate pain relief. Although much progress has been made in the alleviation of pain, the discomfort of minor gynecological surgical techniques has been minimized.

Trilene is employed in obstetrics as an incomplete or partial general anesthetic to lessen the pain of labor. Satisfactory analgesia has been reported with the drug in 80 per cent of cases.[1, 2, 3] It is safe, efficient, agreeable and adapted to short surgical procedures which do not require muscular relaxation.

Material and Procedures

There were 65 women on whom Trilene was used for a total of 198 tests or an average of 3 procedures per patient. The youngest patient was 19 years of age and the oldest 38; the median was 28 years. No adjunctive medication was given except in one case. The Duke inhaler[4] was employed. The technique of administration of Trilene has been discussed in detail by Flowers.[3] The agent was self-administered and care was exercised initially to instruct the patient in its use. The first two or three breaths were taken with the mouth open and the mask loosely applied to the face. A low vapor cone was employed until the patient became accustomed to the smell. The concentration of Trilene was adjusted until the desired depth of analgesia had been reached.

Results

There were no untoward reactions. Only a few patients remained five to ten minutes after the cessation of the anesthetic, to get rid of a "lightheaded" or "dazed" feeling. In 10 per cent there was a lack of pain relief. A few patients considered the gas objectionable.

Seventy-six tubal insufflations were performed on 38 patients. Thirty kymographic tracings showed normal tubal function and patency at 100 mm. Hg, or below; 22 tests revealed patency from 101 to 180 mm. Hg; 4 tests disclosed patency over 180 mm. Hg. Tubal occlusion was present in 20 of the recordings. Repeated insufflations were undertaken in 15 cases and of these 6 women had two insufflations; 2 patients had three insufflations; 7 women had four to six insufflations (Table I). Kymographic oscillations did not appear to be affected by the drug. The subjective symptom of shoulder pain was not obliterated. Trilene may not be a valuable adjunct for those who localize the site of tubal occlusion by referred pain in the pelvis.

Thirty-eight women yielded 101 endometrial specimens (Table I). Biopsy examination was repeated on 24 patients. In 7 cases two specimens were

*The majority of these cases were obtained from the records of the late Dr. Samuel L. Siegler.

taken; in one case three specimens were taken; 16 women were subjected to endometrial examinations from four to six times.[5] No increased uterine bleeding was observed.

Hysterosalpingography was performed on 14 patients. Bley stem pessaries were inserted into 3 women. Cervical dilatation was done in 3 cases and stilbestrol was injected into the cervix of one patient.

Comments

Our goal was to eliminate pain and discomfort without increasing the risk to the patient. The nature and site of the operative procedures described required partial or incomplete anesthesia for a short time.

Walker and Stout[6] analyzed the effect of various analgesic and anesthetic agents on tubal motility and observed that uterotubal spasm tended to be abolished by ether, chloroform, and trichlorethylene. Whether the spasm was relieved by alteration of the psychological reaction, whereby fear and tension were replaced by relaxation, or by a direct effect of the agent on the uterotubal junction, was uncertain. Trilene was valuable when repeated insufflations were required to maintain patency following tubal plastic procedures or to establish patency in the conservative therapeutic management of diseased Fallopian tubes.

TABLE I. SUMMARY OF PROCEDURES PERFORMED UNDER TRILENE ANALGESIA

NO. OF TESTS PER PATIENT	TUBAL INSUFFLATION	ENDOMETRIAL BIOPSY	HYSTEROSALPINGOGRAPHY
1	24	14	14
2	6	7	
3	2	1	
4	3	11	
5	2	4	
6	2	1	

Most women have pain when an endometrial biopsy specimen is procured. Patients were more willing to return for repeated studies, reassured that little discomfort would be encountered. More adequate samples were obtained because of increased cooperation by the patient and more deliberation by the surgeon.

Analgesia is desired in cervical dilatations, occasional pelvic examinations, and several other gynecological procedures.

Trilene has a high index of safety and it can be self-administered. Although the limits of variation of the Trilene vapor-air mixture are great, with reasonable caution and preliminary explanation to the patient, potential dangers can be eliminated. It should, however, be avoided in patients who have cardiac arrhythmias or myocardial damage.[7]

Summary

Trilene is a valuable adjunct for pain relief in gynecological office surgery.

We acknowledge with thanks the generous supply of Trilene (trichlorethylene) from Dr. S. H. Jaros of Ayerst, McKenna and Harrison Limited.

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MALIGNANT THECOMA WITH METASTASES

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In 1932 Löffler and Priesel[1] introduced the concept of the theca-cell tumor, summarizing six cases of this ovarian tumor. Only one, however, was considered malignant because of the presence of ascites, adhesions, necrosis, cellular pleomorphism, and excessive mitosis. Since then, over 125 additional theca-cell tumors have been reported but only five of these have been designated as malignant.

Huber,[2] in 1937, described a thecoma which he considered malignant on the basis of excessive cellularity and mitosis as well as the presence of giant cells.

A third case, reported by Geist and Gaines[3] in 1938, was regarded as malignant because of ascites, adhesions, metastatic nodules, cellular pleomorphism, and extensive mitosis.

The next malignant case was not reported until 1950 when Carter and associates[4] established their diagnosis by the presence of theca-type cells with demonstrable intracellular lipid in metastatic nodules.

In 1951, Proctor and others[5] described a theca-cell tumor of which the malignancy was manifested by both operative and autopsy findings.

Then Rogers,[6] in 1952, reviewed the literature and added the sixth case, a theca-cell tumor with metastases to the broad ligament.

The following is the account of an additional case, the seventh in the literature, of a malignant theca-cell tumor.

Presentation of the Case

The patient* was a 39-year-old white nulliparous housewife with the chief complaint of pain in the suprapubic area aggravated by urination and bowel movements. Melena had been present for five days prior to admission. There had been no alteration in the menstrual history and a normal period had occurred in the month before admission. Physical examination revealed a well-nourished woman with tenderness and rigidity in the suprapubic area. There was normally active peristalsis. No fluid or masses were noted. The results of a pelvic examination indicated that there were a fibroid uterus and a right ovarian cyst. There were 3.75 million erythrocytes and 9,400 leukocytes per cubic millimeter of blood. Urinalysis gave no abnormal findings.

*Service of Dr. J. P. Kerr.

At laparotomy, 2,000 c.c. of bloody fluid was removed by suction and a right ovarian cyst was found. The omentum and the mesentery were involved in a mass of cancer tissue. A right salpingo-oophorectomy and omental biopsy were done.

Fig. 1.

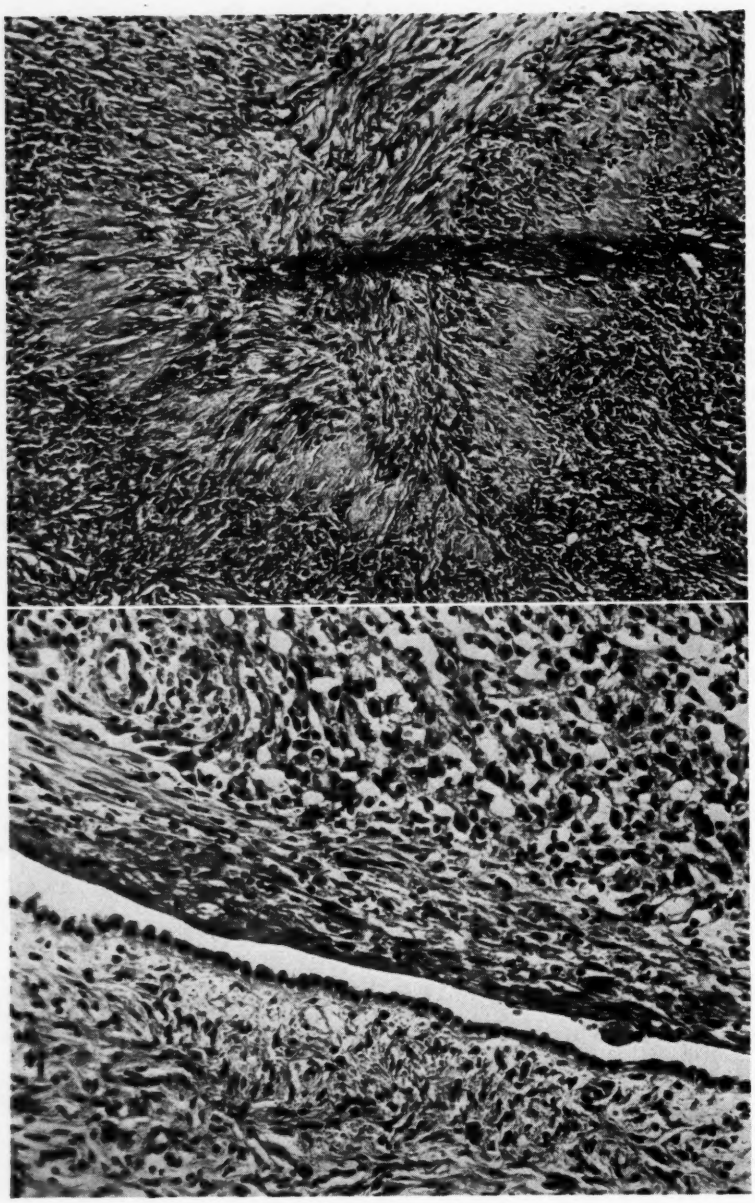

Fig. 2.

Fig. 1.—Section of ovary taken through that portion of the tumor which exhibits a well-defined spindle-cell morphology and the formation of a hyaline plaque. (Hematoxylin and eosin stain; ×150; reduced ¼.)

Fig. 2.—Section of ovarian cortex with normal stroma and covering of swollen surface cells. Overlying the ovarian surface is a mass of tumor tissue with a pleomorphic type of cell. In other fields this tumor is continuous with the ovarian stroma. (Hematoxylin and eosin. ×300; reduced ¼.)

Two days postoperatively, the patient became jaundiced. Four days postoperatively, the temperature rose to 104° F. and the abdomen became distended. The temperature remained elevated and the patient died nine days postoperatively. Postmortem examination was refused.

Description of the Tumor.—The surgical specimen consisted of an ovary with attached Fallopian tube and three pieces of omentum. The ovary, 4 by 6.5 by 8.5 cm., had a cystic and a solid portion, the latter measuring 2.2 by 4.5 by 4.5 cm. The external surface was partially covered by a smooth serosa and partially by nodular, granular, friable growth 1 to 2 mm. in thickness. Section revealed a solid, yellow-white tumor with scattered, poorly defined, yellow nodules 3 to 4 mm. in diameter. The cystic portion had a flattened oval shape and measured 4 by 4 by 5.5 cm. Its outer surface was dull, gray white, and covered with fibrin strands and nodular friable growth similar to that on the solid portion. The cyst wall varied from 2 to 7 mm. in thickness and the inner surface was gray blue, trabeculated and irregular, but without papillae.

The pieces of omentum each measured approximately 1.5 by 3 by 4 cm. and were firm, friable, and of a brown-yellow color. Section showed replacement of yellow, translucent fat by opaque, gray-white, nodular tissue.

Microscopically, the tumor presented a very cellular picture containing areas of necrosis and hemorrhage. In the cellular area were found elongated, spindle-shaped cells and nuclei arranged in interwoven broad bands or bundles. This pattern gave way to areas where the cells were generally more ovoid and pleomorphic with clear cytoplasm and large hyperchromatic nuclei. The serosa of the ovary was covered by masses of such ovoid and pleomorphic cells. There were but a few of the characteristic hyaline plaques discernible in the sections. The aniline blue stain indicated the presence of intercellular collagenous fibers. The cytoplasm was vacuolated in the areas of interwoven bundles of spindle-shaped cells, and it was here that sudan IV-stained frozen sections demonstrated an abundance of fat droplets. Although much of the fat appeared to be intracellular, its extracellular occurrence could not be excluded. Very fine intracellular fat droplets, less numerous, were also found in many of the more pleomorphic cells. The fat droplets were in greatest concentration at the periphery of necrotic areas.

There was extensive replacement and infiltration of the omental fat by elongated plump cells, spindle-shaped cells, and pleomorphic cells arranged in irregular masses. Many, but by no means all, of these cells also demonstrated intracellular fat in the form of fine droplets.

Comment

From the original description the theca-cell tumor is given as a solid or cystic tumor with a yellow color on the cut surface. Microscopically, there are dense bands of broad or spindle-shaped cells with elongated or vesicular nuclei rich in chromatin. The cytoplasm of many of these cells contains vacuoles. Mallory stain shows fine intercellular fibrillae and sudan stain demonstrates the presence of both intracellular and extracellular fat droplets. As the periphery of the tumor nodule is approached, increasing amounts of a cellular and hyaline matrix are found leading to formation of hyaline plaques.

All these criteria were found in the present case together with additional features indicative of malignancy. These include pleomorphic cell structure, necrosis, excessive mitosis, invasion of the ovarian serosa, and omental tumor masses with a cellular structure similar to that of the primary tumor.

The belief that the theca-cell tumor and the granulosa-cell tumor are very closely related seems justified. Novak[7] believes both tumors are derived from a common source, the ovarian mesenchyme. In the tumor reported here many cells, particularly in the metastases, were plump, with more resemblance to

granulosa cells than to the spindle-shaped theca cells seen near the hyaline plaques. Dr. Novak[8] considered this neoplasm an anaplastic type of granulosa-thecomatous tumor.

In accepting the concept of a common origin for the cells present in malignant theca-cell and granulosa-cell tumors, the question may arise whether or not it is proper to separate these two neoplasms as entities. This question is appropriate since both cell types may be present in either of these tumors; as long, however, as the benign thecoma and the granulosa-cell tumor are accepted as separate pathological entities, it seems logical to recognize also the malignant variants of these tumors.

Summary

A case of a malignant theca-cell tumor of the ovary with metastases is described. This is the seventh of its kind to be reported in the literature.

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VESICOUTERINE FISTULA ASSOCIATED WITH A CALCIFIED LEIOMYOMA

Case Report

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PARTIALLY calcified uterine leiomyomas are frequently observed among fresh surgical specimens. A totally calcified tumor is much less common, and is usually a pedunculated fibroid which has undergone hyaline degeneration because of reduction in its blood supply.

A calcified uterine fibroid with a fistulous tract between the myoma and the urinary bladder is infrequently encountered. Fistulas of this type were first described by M. Louis[1] in 1752. In 1901 M. Guibe[2] listed four cases. A fifth report was published by Weiner, Burke, and Sherman[3] in 1950. A uterovesical fistula associated with a calcified uterine fibroid was treated recently at Wilson Memorial Hospital.

C. R., a 41-year-old white nullipara, was first admitted in 1932, complaining of weakness, dysmenorrhea, irregular menses, and a sensation of fullness in the lower abdomen. Past medical illnesses included a long history of constipation, urinary frequency, and nocturia. A uterine suspension and appendectomy had been done in 1920. Physical examination revealed an obese white woman with an enlarged, firm, nodular uterus. A diagnostic curettage was performed and a large amount of polypoid endometrium obtained. The tissue was reported as "infected endometrium." Radium was applied to the uterine cavity for a total of 2,400 mg. hr. in an attempt to control the menorrhagia.

Eight years later (1940) she was readmitted because of irregular vaginal bleeding, dizziness, fainting, nausea and vomiting. A dilatation and curettage provided no endometrium for examination.

She continued to spot intermittently, and on Oct. 13, 1948, an endocervical polyp was removed. Histologic examination disclosed adenocarcinoma arising in a benign endocervical polyp. Because of her obesity, radium therapy was considered the most practical, and a total of 5,600 mg. hr. was administered. At the time of application of radium the vagina was found to be constricted and the cervix was flush with the vault.

She was admitted again on Oct. 18, 1949, because of pain in the left lower quadrant of the abdomen, severe dysuria, marked urinary frequency, and nocturia. In addition she had noticed blood and gravel in the urine. Cystoscopy under general anesthesia showed the bladder to be lined with an adherent, fuzzy, white, gritty substance. The underlying bladder wall appeared injected and bled easily. The capacity of the bladder was less than 100 c.c. Enterococci, coliform bacilli, and *B. proteus* were consistently reported in the urine cultures. She improved subjectively following oral Aureomycin and bladder irrigations but cystoscopic examination showed the calcification to be unchanged. An attempt to curette the mucosal calcifications was abandoned because of adherence and fear that the bladder wall would be

perforated. Polypoid proliferations which developed on the right side of the bladder vault were thought to be extensions of the previously treated cervical adenocarcinoma, but no tumor was evident on histological examination. She was discharged on Dec. 18, 1949.

After a brief period of subjective improvement she was readmitted on Sept. 30, 1950. In addition to the bladder-wall calcification, a 2.5 cm. vesical calculus was found and removed by litholapaxy. Intravenous pyelograms revealed a negative upper urinary tract, a bladder of 60 c.c. capacity, and a calcified uterine fibroid about 7.0 cm. in diameter in the upper right side of the pelvis (Fig. 1). Her symptoms regressed when re-treated with bladder irrigations, and she was discharged from the hospital.

Fig. 1.—Film of abdomen showing calcified uterine fibroid.

She was readmitted on Dec. 5, 1950, for cystoscopy and was treated with further irrigations. Endoscopy one month later showed disappearance of most of the calcification, although an ulceration on the bladder dome persisted. For the next 40 days 100 mg. of cortisone was administered daily. There was an increase in bladder capacity to 200 c.c., and subsequent cystoscopic examination showed absence of encrustations.

Examination on Aug. 13, 1952, revealed that the ulceration had healed, but large amounts of cloudy material exuded from a small opening in the dome of the bladder. A catheter was inserted approximately 10 cm. into the sinus tract and Skiodan was injected. A calcified mass with a cavity 6 to 7 cm. in diameter was demonstrated on radiography. Although reasonably comfortable on clinic visits, she complained of recurrent frequency, dysuria, and chills. She noted during these attacks that the urine was clear; the appearance of dirty-brown urine was associated with relief of symptoms.

One year later (Aug. 11, 1953) she was admitted for repair of the now recognized vesicouterine fistula. The uterus was still somewhat enlarged and irregular in shape. Rectal examination disclosed an irregular firm mass attached to the uterus and lying in the cul-de-sac of Douglas. The urine was cloudy, highly concentrated, and loaded with white and red blood cells. Fasting blood sugar was 295 mg. per cent, nonprotein nitrogen, blood chlorides, serum protein, and albumin-globulin ratio were normal. Insulin was administered preoperatively.

Under Pentothal-nitrous oxide-ether anesthesia both ureters were catheterized, and, after skin preparation, a 35 cm. suprapubic Cherney-Bardenheuer incision was made. The irregular uterus was attached to adjacent bowel by a few filmy adhesions. A fibroid approximately 6 cm. in diameter projected from the level of the cervix into the posterior cul-de-sac.

Fig. 2.—Uterus with calcium deposits within uterine cavity. Pointer on posterior fibroid indicating level of fistula.

Irradiation had sclerosed the bladder; the uterine vessels were obliterated due to cervical scarring. The vesicouterine peritoneal fold was incised and the bladder was dissected from the cervix. At this point the fistulous tract entered the vesicouterine junction, draining the necrotizing calcified fibroid into the bladder. Two interrupted sutures of No. 000 chromic catgut were placed to cover the fistulous opening. The uterus containing the calcified fibroid was excised just below the level of the internal os; both tubes and ovaries were included. Ureteral catheters were palpated and there was no evidence of injury.

Recovery was complicated by atelectasis and a subcutaneous wound abscess. A retention catheter was left in place for six days. On Sept. 27, 1953, when discharged, she was able to retain the urine for two to three hours, and had nocturia three to four times. This improved, and at the last examination she retained urine for four hours and had nocturia only once.

The pathological specimen showed a supracervically amputated uterus that measured 11 by 9 by 5 cm. The outline was distorted by several leiomyomas. The cavity contained thin irregular layers of hard, yellowish, calcified material (Fig. 2). The endometrium was soft, focally hemorrhagic, and showed a polypoid bridge in the region of the fundus. Several small polypoid projections were seen elsewhere. The myometrium was soft and gray except for the intramural leiomyomas. Diagnosis: leiomyomas of the uterus, severe chronic active myometritis, severe acute and chronic endometritis with ulceration and calcification and polypoid overgrowth; calcareous mass in the endometrial cavity. There was no evidence of neoplasm in the sections studied.

Comment

Cases of vesical calculi forming in the presence of irritation from adjacent calcified uterine fibroids have been reported by Boehm,[4] and by Kelly and Cullen.[5] We believe that a similar condition existed in this case with resulting calcification and stone formation.

The formation of the fistulas has been postulated to be due to pressure necrosis in the case of fixed tumors, especially when there is compression by the fibroid against some bony part. The presence of constant irritation from infection in an area of decreased resistance and devitalized tissues has been thought to be the etiological factor in a situation where pedunculated movable leiomyomas were found.

In our opinion several factors were involved in the formation of the fistula in this patient. The uterine vessels in the region of the fibroma were markedly sclerosed. The tumor, in turn, nestled posteriorly, forcing the cervix against a bladder which had been compromised by two courses of radiation. The cervical canal was completely stenosed following radium therapy, and, because of this, the necrotic debris from the calcified myoma took the nearest exit, i.e., through the previously irradiated urinary bladder.

Summary

A sixth case of vesicouterine fistula associated with a calcified uterine fibroma has been added to the literature. Radiation cystitis and pressure necrosis were considered to be important factors in the formation of the fistula.

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A NUTRITIONAL PROBLEM IN PREGNANCY RESULTING FROM EXTENSIVE RESECTION OF THE SMALL BOWEL*

Case Report

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THE following case report has to do with a patient who had extended resections of the small bowel for terminal ileitis, following which there were serious nutritional problems. These resolved in part when the patient became pregnant.

The case is illustrative of the tremendous stimulus which pregnancy constitutes to nutrition in general, and the amazing adaptiveness of the human organism.

Mrs. G. C., aged 23 years, was referred to the obstetrical consultant on June 20, 1952, by her attending internist with the question as to whether pregnancy should be continued in the face of grave nutritional problems. She was 23 years of age, had been married nine weeks, and had her last menstrual period on May 10, with the expected date of confinement Feb. 20, 1953. She had been feeling surprisingly well since the onset of pregnancy, and was quite eager to continue with the pregnancy if her medical advisers considered it permissible.

She gave the history of having had four operations: first, an appendectomy early in life, and then three successive intestinal resections for terminal ileitis at 17, 18, and 20 years of age. The final operation had left her with an estimated 2½ feet of small intestine, consisting of duodenum and proximal jejunum anastomosed to the cecum. At 7 years of age she was also presumed to have had a streptococcic nephritis with apparently no sequelae. The systemic review was essentially normal.

The problem of maintaining nutrition following these several operations had been quite a serious one. This case has been reported previously because of the beneficial effect apparently produced by the administration of testosterone as an anabolic agent. She generally had two to four soft stools daily, containing significant amounts of undigested fat and meat fibers as well as undigested vegetable material. Her weight was maintained at 90 to 95 pounds, although her best previous weight had been 105. Despite her general feeling of well-being, it seemed fairly evident that the patient was in precarious balance. A relatively mild upper respiratory infection lasting three to four days resulted in a weight loss of 5 pounds, and a short period of diarrhea, presumably viral in origin, resulted in a somewhat greater weight loss. It was thought that it might require as long as a month for her to regain the lost weight.

The patient appeared to feel better when receiving testosterone, the dose of which was finally reduced from 50 mg. to 5 mg. every other day. The latter dose appeared to be so small that a placebo was administered, but the patient became depressed, lost her appetite, and some weight, so that the small dosage was continued by buccal tablet until her pregnancy. The role of the androgen in the treatment of this case is difficult to evalu-

*Presented at a meeting of the Obstetrical Society of Philadelphia, Jan. 7, 1954.

ate. Many steroids have in common the ability to produce a euphoria which may, at times, be striking. It may well be that the beneficial effect which this patient experienced was due to the improvement of her morale, her appetite, and her general feeling of well-being, or, as seems possible, the anabolic effect of the steroid produced changes in the mucosa of the intestinal tract permitting a more normal digestion and absorption.

The patient had been advised some time previously that she should not become pregnant if marriage ever occurred. Since she had at one time been informed by a third physician, however, that she had an infantile uterus and could not conceive, she was not very careful about contraceptive measures in her early married life, and the unexpected and undesired event of pregnancy had occurred quite promptly.

Physical examination by the obstetrician at this time revealed a rather normal-appearing, slightly built young woman with a weight of 101 pounds, a blood pressure of 110/60, a hemoglobin of 70 per cent, and a urine which was free of albumin and sugar and of normal specific gravity. The breasts revealed the typical signs of pregnancy. Inspection of the abdomen revealed the four previously described abdominal incisions, and no local masses or areas of tenderness were noted.

Upon pelvic examination, the external genitals were normal and the uterus was slightly enlarged in correspondence to the period of amenorrhea. The pelvis itself appeared to be gynecoid and fairly ample.

Because of the present appearance of well-being and the great desire of the patient to continue the pregnancy if at all feasible, it was recommended that pregnancy be allowed to proceed, and that the reaction of the patient be observed carefully in the ensuing weeks and months. It was felt that, if necessity required, the pregnancy could be more readily terminated by abdominal hysterotomy than by induction of abortion in a young primigravida, and that in emergency the patient's nutrition could be maintained by parenteral feeding.

Very shortly after this pregnancy begun, the patient noted a clear-cut change in her bowel habit. She had but one stool a day, and that was more nearly formed than previously. It was our impression on microscopic examination that there were less fat and fewer undigested meat fibers but considerable amounts of undigested vegetable material remained. Throughout her pregnancy, the patient had a voracious appetite, and consumed 4,000 to 5,000 calories daily. The diet was supplemented with large doses of calcium gluconate because of the common occurrence of hypocalcemia in patients with deficient intestinal absorption. The weight increased steadily from 101 pounds to 115 pounds at term. On one occasion, when the patient experiened a brief episode of diarrhea, she lost four pounds in two days, but this was gradually regained in the subsequent two weeks. The blood pressure varied from 110/70 to 120/75, and only on one occasion reached 130/78. Albumin and sugar were consistently negative. The fundus measurement of the uterus rose steadily to 32 cm.

On Feb. 24, 1953, the patient had an uncomplicated spontaneous labor and delivery with blood loss somewhat less than the average. Nitrous oxide and oxygen were used for delivery and pudendal block for episiotomy and repair. Because of slight hypocalcemia, the patient was given an intravenous drip of Ringer's solution with calcium gluconate during the course of labor. The baby's birth weight was 6 pounds, and examination by the attending pediatrician revealed it to be a sound, normally developed female fetus.

The subsequent puerperal recovery of the mother was quite satisfactory, and she was discharged on the sixth day. Postnatal examination performed six weeks later showed her weight to be 96½ pounds, the abdomen free of any palpable masses or tenderness, and the pelvic organs well involuted with slight erosion of the cervix. The catheterized urine specimen was clear; the hemoglobin was 70 per cent. Coagulation of the cervix was performed at a subsequent visit. The patient was provided with a contraceptive device. She continued to feel well, despite her loss of weight, although she did experience some fatigue as a result of taking care of her household and child.

Fig. 1.

Fig. 2.

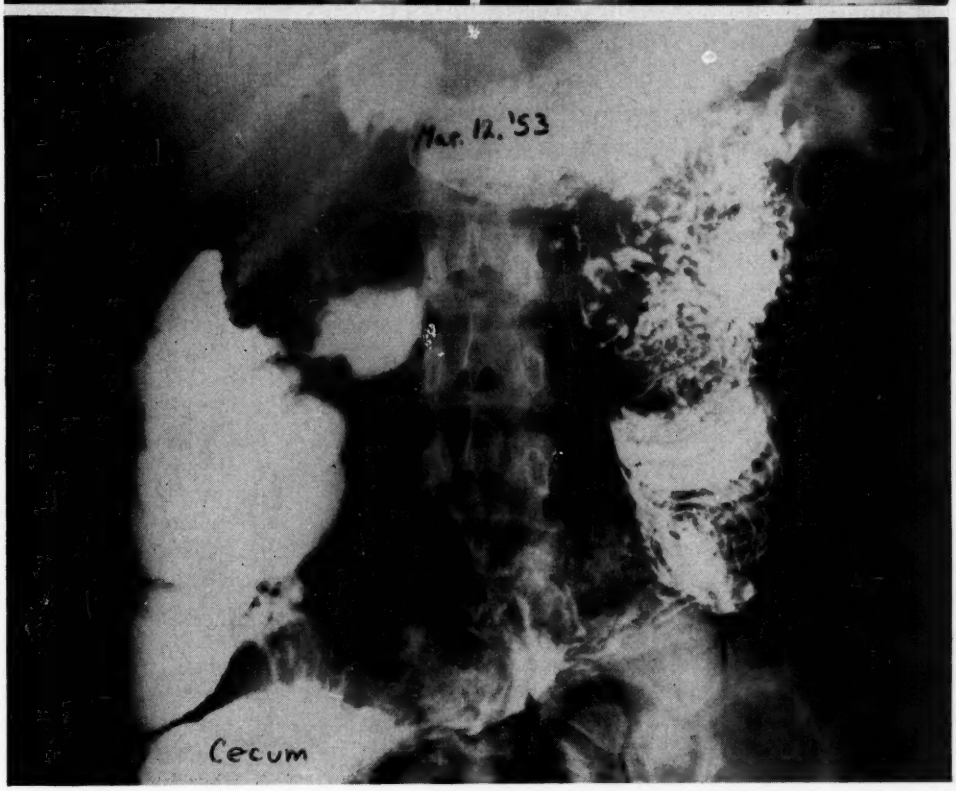

Fig. 1.—Radiograph taken following delivery. Note the markedly shortened small intestine as seen in the film on left. This shows no change from previous examinations. The film on the right shows the intussusception described in the text.

Fig. 2.—Radiograph of the small intestine showing entero-enteric intussusception.

There has been no evidence of a recurrence of her intestinal disease after the third resection. The remaining small intestine became enlarged so that it was two and one-half to three times the normal diameter, but it was obvious that this was not the result of any obstructive lesion. Fig. 1 shows the appearance of the intestine soon after the termination of her pregnancy. The small intestine is shortened but dilated. The appearance is unchanged from previous examinations. During the course of this examination, however, an intussusception of the small intestine occurred. This is shown on the right in Fig. 1, and is better demonstrated in the film reproduced in Fig. 2. It will be seen that the proximal intestine invaginated into the distal jejunum, producing a shortening of 10 to 12 inches. The patient was closely questioned at this time, and on the following day. There were no associated complaints, no pain or cramps, and no blood appeared in the stool. Many additional films were taken in the course of this study which was performed at the Graduate Hospital. No intrinsic disease of the small intestine was demonstrated and it was felt that the intussusception probably resulted from the dilatation of the small intestine. It also seems possible that this phenomenon might well occur intermittently, but cause no vascular occlusion or other disturbance. Entero-enteric intussusception is quite unusual, however, in the absence of intrinsic small-intestinal disease.

The patient had been asked to return for further study. She informed us that a second pregnancy has occurred. She has again experienced a definite change in bowel function, improvement in appetite, and a sense of well-being.

The remarkable improvement which occurred in this patient's digestive-tract function with pregnancy was somewhat unexpected. She was barely able to compensate for the small-bowel deficiency, and she had been in precarious balance prior to her first pregnancy. The beneficial effects of pregnancy were not anticipated, and, indeed, the ability of the organism to adjust to this physiological state has been remarkable.

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CHORIONEPITHELIOMA FOLLOWING A FULL-TERM PREGNANCY

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IT IS in view of the rarity of chorionepithelioma that the present report of the history and treatment of this patient is made.

A 23-year-old white para i, gravida i, was first seen Nov. 14, 1953, with the complaints of dark red vaginal bleeding of six weeks' duration, a nonsanguineous productive cough of seven days' duration, and dull pain in the lower abdomen, bilateral, of several days' duration.

Menstruation began at the age of 14, occurred every 30 days, lasted seven days, and was heavy in amount with occasional clots.

In July, 1952, a normal, term infant was delivered, following an uneventful antepartum course. After delivery of the placenta, hemorrhage occurred which required an intrauterine pack. This was removed after twenty-four hours.

Six weeks post partum, the uterus was retroverted, enlarged, and boggy. During the following month considerable vaginal bleeding occurred. A dilatation and curettage was performed three months after delivery, which revealed necrotic decidua and fibrin but no chorionic villi. Associated with this procedure severe bleeding occurred which required the giving of 1,000 c.c. of blood.

Over the next eight months the menstrual periods were heavier than normal and several days late at times. The period in December, 1952, was reported as having been very heavy. This menstrual behavior continued until one year following delivery, when the patient was examined by another physician who described an enlarged, soft, retroverted uterus, and performed an exploratory laparotomy. A tumor considered to be a fibromyoma was removed from the anterior uterine wall (Fig. 1). The uterine cavity was entered and the endometrium found to be grossly normal. The uterus was suspended.

The postoperative course was uneventful. An Aschheim-Zondek test performed 24 days postoperatively was negative and a Friedman test done 28 days postoperatively was also negative. However, Aschheim-Zondek tests conducted 67 days postoperatively on urine and blood were positive; at 1:100 dilution they were negative.

Physical examination revealed râles over both lung fields which did not clear on coughing. A midline, rounded, slightly movable, firm mass extended 15 cm. above the symphysis pubis. The right uterosacral ligament was indurated and nodular. The cervical canal contained dark bloody mucus. A dark bluish elevated area approximately 1.5 cm. in diameter was noted in the anterior vaginal wall adjacent to the urethral meatus.

Laboratory studies revealed a positive Aschheim-Zondek test on Nov. 16, 1953. A chest x-ray showed multiple areas of extra density throughout. A cervical biopsy showed no chorionepithelioma. The hemoglobin was 8.5 Gm. per 100 c.c., red blood count 3.37 million; the leukocyte and differential counts were normal.

The cough increased greatly with the production of blood-tinged sputum. Dyspnea and cyanosis developed. A blood transfusion of 1,000 c.c. was given. On the fourth hospital day a dilatation and curettage was done, followed by a hysterectomy, bilateral salpingo-oophorectomy and lysis of dense pelvic adhesions, during which procedures 2,000 c.c. of blood was given.

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*Markle Scholar in Medical Science.

The uterus was dark purplish and soft, with an intact serosal surface. It weighed 955 grams (Fig. 2). The right ovary measured 5 by 4 by 3 and the left 6.5 by 4 by 2.5 cm., and each contained numerous lutein cysts. Microscopically, chorionepithelioma was present in the myometrium and in the left ovary. Syncytial and Langhans elements were present throughout the myometrium (Fig. 3). The myometrium also contained numerous areas of hemorrhage and necrosis.

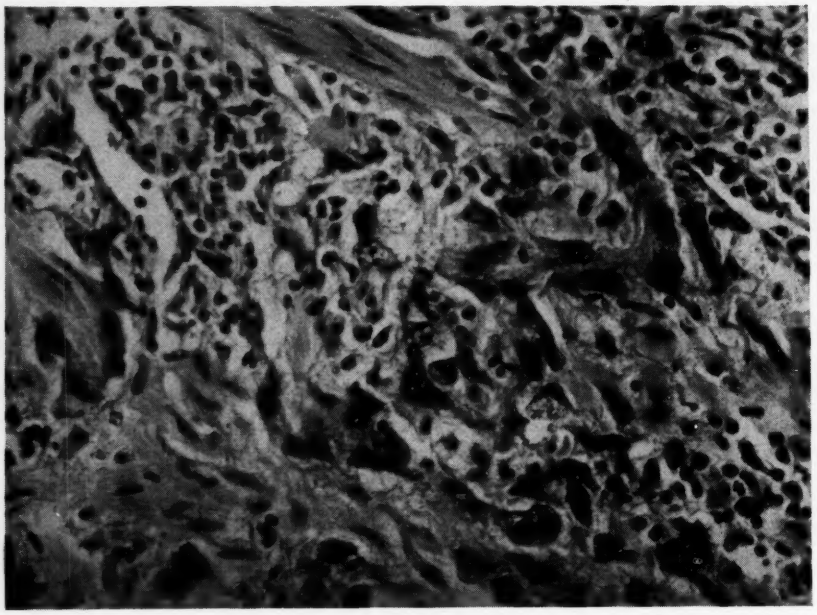

Fig. 1.—Histological appearance of the mass removed from the uterine wall.

Fig. 2.—Uterus, opened; right and left adnexa.

On the first postoperative day an oxygen tent was required on account of dyspnea. Breathing became so shallow, rapid, and painful on the third day that it was agreed upon with the Medical Consultant that cortisone be tried for what it might do in suppressing inflammatory reaction around the pulmonary metastases. The dosage of cortisone was as

follows: 50 mg. orally every 6 hours from the third to the fifth day; 25 mg. every 6 hours from the fifth to the thirteenth day; 25 mg. every 8 hours from the thirteenth to the twenty-first day, when the cortisone was discontinued. Within 12 hours from the start of cortisone therapy, the dyspnea became negligible. The oxygen tent was no longer required. Penicillin was prescribed prophylactically. Testosterone propionate, 100 mg. daily, was given from the third to the twenty-second day.

A course of roentgen therapy was started to the chest and pelvis on the fifth postoperative day. An x-ray of the chest 15 days after the start of roentgen therapy showed no change in the tumor shadows.

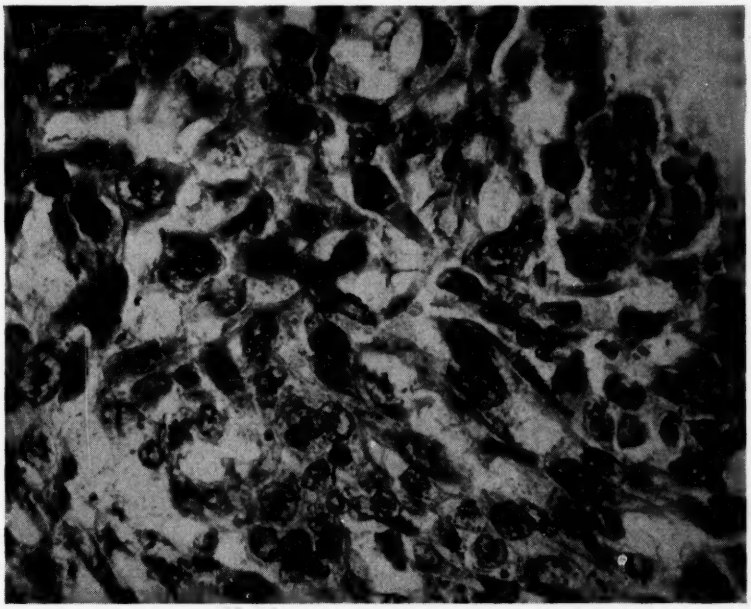

Fig. 3.—Histological appearance of the uterine wall.

By the twenty-second postoperative day vaginal metastases had increased in size and number until the introitus and vagina were almost occluded, a biopsy from which was confirmatory of chorionepithelioma. Except for chest pain and low back discomfort, the patient was asymptomatic and ambulatory until the twenty-eighth postoperative day when respirations became rapid (100 per minute) and shallow with an accompanying techycardia (160 per minute). Death occurred on the twenty-ninth postoperative day. Postmortem examination was not permitted.

Comment

From the history this is considered to be a chorionepithelioma following a normal full-term delivery. As shown by Novak and Seah[1] in 74 authenticated cases, chorionepithelioma following a normal gestation is least common. They reported 29 (39.2 per cent), 28 (37.8 per cent), and 17 (23.0 per cent) cases, respectively, following hydatidiform mole, abortion, and full-term pregnancy. They also found the greatest number of cases reported to be between the ages of 20 and 30 years. From the cases studied by them, there was no indication that increase in parity makes for a greater likelihood of the development of chorionepithelioma. As we have noted, this patient was a primipara, aged 23 years.

The abnormal bleeding at delivery, the enlarged and boggy uterus six weeks post partum, the continued bleeding before and profuse bleeding at dilatation and curettage, and subsequent menorrhagia were compatible with the later diagnosis of chorionepithelioma, even though no indication of the disease was found in the curettings. Of the 74 chorionepitheliomas already referred to, in only 13 was the diagnosis strongly indicated from the curettings. On the other hand, had a dilatation and curettage been performed before the laparotomy, the diagnosis might have been made in this patient.

As illustrated in Fig. 1, the histological slide from the mass removed July 25, 1952, showed fairly extensive areas of syncytial and Langhans elements; no chorionic villi were seen, indicative of the degree of malignancy, as pointed out by Novak and Seah.[1] In the 74 chorionepitheliomas they studied, only one showed chorionic villi.

It has been shown that the best results have been obtained after hysterectomy plus irradiation.[1] Accordingly, the hysterectomy was performed in order to get rid of the primary tumor mass and what stimulating effect it might have had upon the secondary growths, as well as to strive for more effective radiotherapy.

As a palliative measure the course of cortisone appeared to have been definitely beneficial. It was discontinued in view of possible toxic effects.

The efficacy of the testosterone propionate therapy was equivocal. It was used for any possible suppression it might have upon the disease. DeGiorgi[2] reported giving large doses of androgens to a patient with chorionepithelioma for any palliative effect. The treatment was given for two weeks after hysterectomy when the patient died. Duffy[3] reports a case in which chorionepithelioma was in the vagina, ischiorectal fossa, myometrium, and in a single pulmonary area. This patient underwent a subtotal hysterectomy and bilateral salpingo-oophorectomy and was given 100 mg. of testosterone propionate daily for nine months following the hysterectomy. She is reported as living and well five years later.

Even though chorionepithelioma occurs far more often after parturition, abortion, or molar pregnancy, it may develop late in the course of a normal gestation.[4] From the history this may well have occurred in this patient.

Summary

1. Chorionepithelioma was the cause of death seventeen months after a full-term delivery.

2. An x-ray of the chest, taken sixteen months after parturition, showed definite evidence of pulmonary metastases, at which time vaginal metastasis had already occurred.

3. One month prior to death, hysterectomy and bilateral salpingo-oophorectomy were performed.

4. Five days postoperatively, a course of roentgen therapy was commenced, from which there was no discernible change in the pulmonary metastases.

5. Three days following operation, testosterone propionate, 100 mg. daily, was started, with equivocal results.

6. Cortisone, started postoperatively prior to the androgen, was given in an attempt to relieve marked dyspnea through suppression of inflammatory reaction around the pulmonary metastases. The efficacy of its use palliatively was unequivocal.

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BILATERAL DYSGERMINOMA OF THE OVARY WITH PSEUDOHERMAPHRODITISM

Case Report

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THE term "dysgerminoma" was first suggested by Robert Meyer to describe an ovarian tumor that arose from "indifferent germ cells." Supposedly such tumors arise from cells that date back to the undifferentiated stage of general development before such cells become tinctured with either male or female attributes.[1]

Such speculation regarding the histogenesis of dysgerminoma is interesting but unproved, although it is consistent with the fact that an exactly identical tumor is found in the testis. The testicular "dysgerminoma" is usually described as a "seminoma," the two being indistinguishable histologically.

French pathologists earlier had called these tumors ovarian "seminomas" and had supposed them to be derived from testicular elements in the hilum of the ovary. It is certainly possible that dysgerminomas are indeed seminomas derived from persistent male tissue in an indifferent bisexual gonad. The case of hermaphroditism we are to present, with many external masculine characteristics, appears to give added weight to this theory. The early age at which this tumor occurs, the very frequent association with hermaphroditism, and the preference for the right ovary, all suggest a relationship with some developmental disturbance.[2]

Novak has emphasized that sex abnormalities are not influenced in any way by the removal of the tumor. Most tumors of this type occur in ostensibly normal women, and there have been many reports of dysgerminoma in women who have borne children before or after operation for removal of the tumors. There is a considerable incidence of associated hermaphroditism, however, some with poorly developed sex characteristics, and there have been three instances of associated true hermaphroditism (Polano, Aschkanazg, Reverdin).

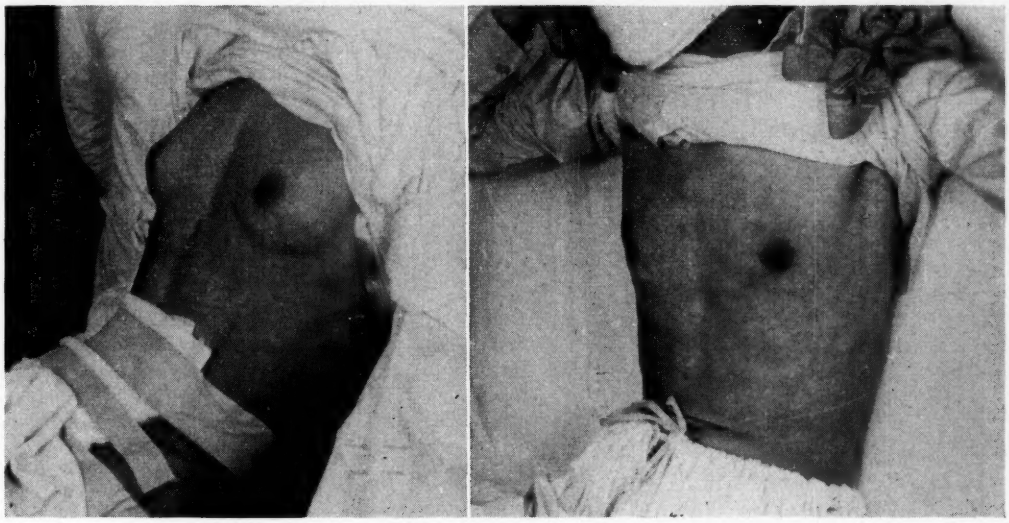
Case Report

A very nervous, slender, 21-year-old young man was admitted to the United Christian Hospital with a chief complaint of abnormal breast development. Since childhood he had been regarded as a male and his life pattern was masculine, but since puberty he had been constantly embarrassed by the increasing size of his breasts. As a baby he had submitted to an operation to straighten the penis, but he had always passed urine from the angle between penis and scrotum. He was able to achieve satisfactory penile erection.

Physical examination revealed a fairly well-developed young man of masculine type build. He had a light beard, hirsutism of male type, and moderately low-pitched voice.

Breast development was marked, and typically female (Fig. 1, *A*). Abdominal examination was negative. The penis was relatively well-developed and a scar along the ventral surface indicated the site of previous surgical chordee correction. The urethral orifice was located at the penoscrotal angle and the scrotal folds were tight, resembling the female vulva. No testicles were palpable in the scrotum or in the inguinal canal (Fig. 2). A flat plate of the abdomen revealed two calcified masses in the pelvis in a position corresponding to the normal location of ovaries. Blood and urine examinations were normal.

First a laparotomy was performed to explore the pelvis. The radiopaque masses seen on x-ray proved to be enlarged, massively calcified ovaries. Poorly developed Fallopian tubes were found, with a hypoplastic uterus and vestigial vagina. All these structures were removed (Fig. 3). The left ovary was free and more cellular, whereas the right ovarian mass was densely calcified and bound down by numerous adhesions to adjacent bowel and pelvic floor. No other gonadal tissue could be found in the pelvis and there was no evidence of tumor metastasis. Recovery from the operation was uneventful.



A. *B.*

Fig. 1.—*A*, Breast development before simple bilateral mastectomy.
B, Postoperative photograph before removal of sutures to demonstrate small areolar incisions.

Following this discovery of a complete female reproductive apparatus it became obvious that our patient was actually a female pseudohermaphrodite, and not a male with gynecomastia, hypospadius, and cryptorchidism. Meanwhile, the patient was most eager to get on with the elimination of his principal problem, the enlarged breasts.

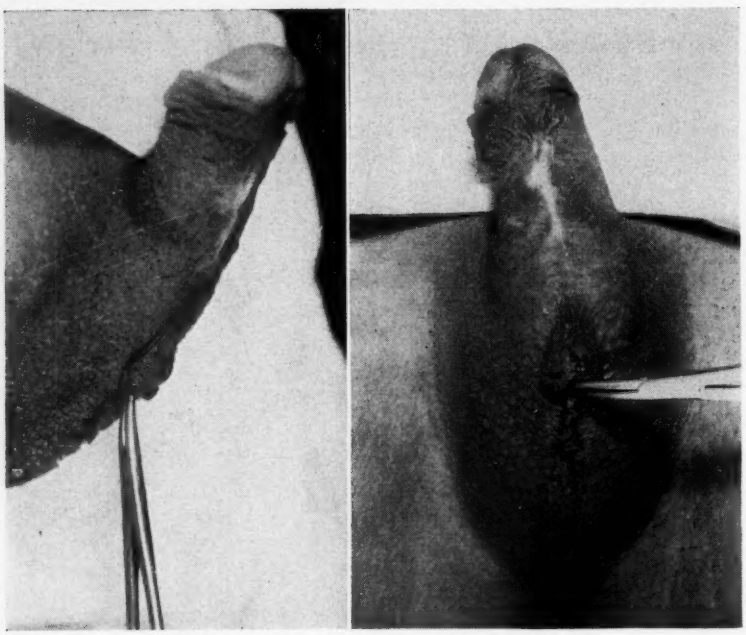
Therefore, nine days after the panhysterectomy, a simple bilateral mastectomy was performed through small arcuate incisions along the inferior margin of each areola (Fig. 1, *B*). It is surprising how much breast tissue can be removed through such small incisions without morcellation, and with no significant scar. At the same time depot testosterone was implanted in the left pectoral muscle. The patient was discharged eight days later with wounds well healed.

Gross tissue examination showed a rather marked dissimilarity between the two ovaries. The left was 3.5 cm. in diameter, rock hard, rough, and pale white in color. It was cut with difficulty and found to be almost completely calcified, with a few cystic areas filled with gray exudate. The right ovary was 2.5 by 3 by 2.5 cm., rubbery in consistency, with a smooth lobulated surface. The cut surface was grayish pink, with multiple areas of necrosis and calcification. Tubal and uterine tissues were typical and breast tissue was grossly normal.

Microscopic examination of the tissues was reported as follows by the pathologist:

Ovarian tumors: Notwithstanding some equivocal evidence, we believe the ovarian tumors to be dysgerminomas. They show a marked tendency to calcification in some areas. Nothing is found in any way to suggest arrhenoblastoma (Fig. 4).

Fallopian tube: Normal. It presents a degree of development like that of the isthmian portion of the tube of a twenty-year-old girl.



A. *B.*

Fig. 2.—The external genitals. A mosquito hemostat indicates the external urethral orifice.

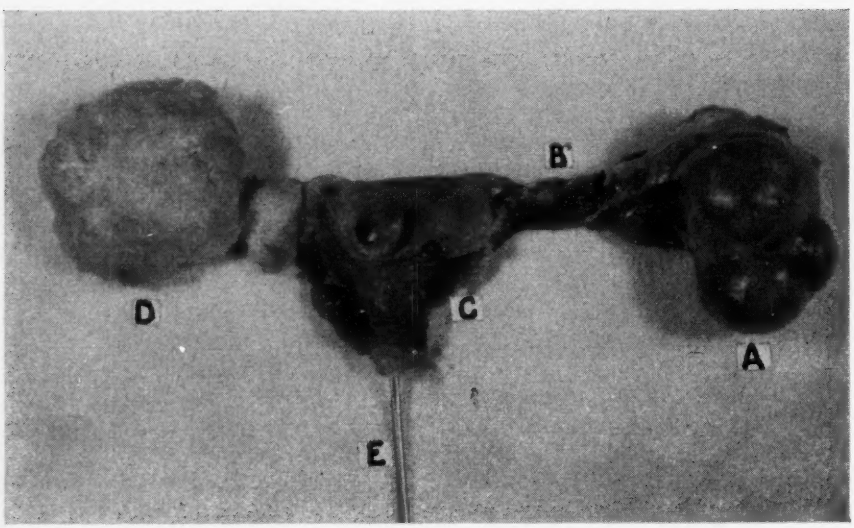


Fig. 3.—Tissues removed from pelvis. *A*, Left ovary. *B*, Fallopian tube. *C*, Hypoplastic uterus. *D*, Right ovary. *E*, Probe in cervix.

Uterus: Hypoplasia. There are cystic glands in the endometrium. The epithelium shows mild proliferative changes (Fig. 5).

Mammary Gland: A resting gland with abundant fibrosis. There is no proliferation of ducts. The appearance is that of a virginal breast. Nothing is found to suggest gynecomastia.

Diagnosis: Pseudohermaphroditism feminus externus with bilateral ovarian dysgerminomas.

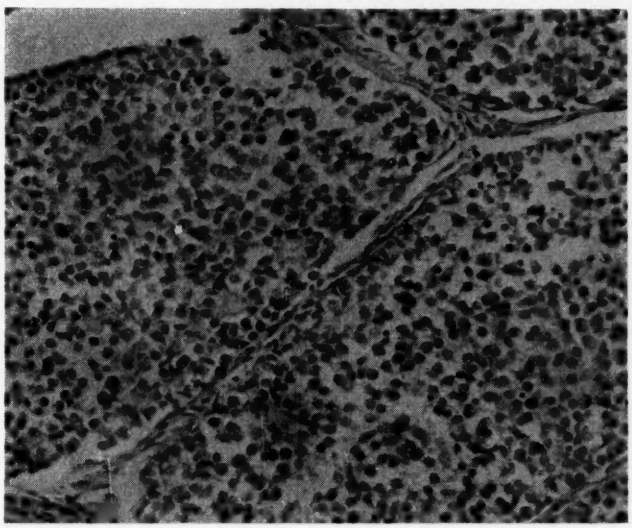


Fig. 4.—Photomicrograph of tissue from left ovary typical of dysgerminoma. There are large round and ovoid cells with abundant, clear, very pale-staining cytoplasm. Cells are arranged in nests separated by fibrous tissue septa, with extensive lymphocytic infiltration.

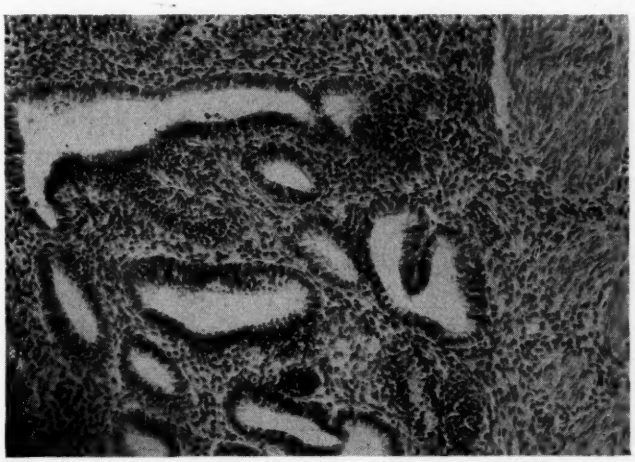


Fig. 5.—Section of uterus showing well-developed endometrium and myometrium.

Summary

We have presented a case of mistaken sexual identity that proved to be a true female with bilateral ovarian dysgerminomas. The patient had sufficient male sex characteristics to have lived a successful, but rather complicated,

male existence. Normal female breast development led the patient to seek medical advice. The penis was in fact a hypertrophied clitoris, the urethral orifice was in the normal female position, and the empty "scrotal folds" were actually vulva. We altered this patient's status surgically to improve his masculinity and eliminate most of his female endowments. Correction of the "hypospadius" is contemplated in the future.

I wish to thank Dr. H. M. Selzer for referring this interesting patient. I am indebted to Dr. Carl Vernon Weller, Pathologist, University of Michigan, for his microscopic tissue studies, and to Dr. Denton Kerr, Gynecologist, Houston, Texas, for his surgical assistance; also to Inez Porter, Department of Medical Photography, St. Luke's Hospital, Chicago.

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ACUTE INTERMITTENT PORPHYRIA COMPLICATED BY PREGNANCY*

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THERE are about 300 cases of porphyria reported in the literature and of this very small group there are no more than 10 in which the disease was complicated by pregnancy.

Nesbitt[2] summarized the historical aspects and classification of porphyria and reported 2 cases of acute porphyria associated with pregnancy. In one patient, spontaneous abortion occurred at about eight weeks and before the diagnosis of porphyria had been established. In the second patient, porphyria was asymptomatic; pregnancy was of twelve weeks' duration, and there was no follow-up report.

Linas and associates[3] reported pregnancy in a patient with chronic porphyria. During pregnancy, she experienced exacerbations of the cutaneous lesions and an increase in porphyrin excretion. She was delivered normally and subsequently improved.

Coleman[4] reported upon a pregnant patient with acute porphyria in whom abdominal symptoms resulted in an exploratory laparotomy. She improved after the first trimester and was delivered by cesarean section because of a central placenta previa.

Freedman and co-workers[5] reported upon a patient with severe acute porphyria who had become pregnant during a brief remission. This patient carried to term despite the severity of the disease and was delivered normally.

Little and Palmer[6] reported a case of acute porphyria complicated by pregnancy and with a fatal termination. They discussed 4 additional similar cases.

The porphyrins are pigments which occur normally in both plant and animal life. Actioporphyrin is the pigment base of chlorophyll in plants. Protoporphyrin is the porphyrin of blood pigment which combines with iron and globin to form the basis of hemoglobin. In animals, coproporphyrin occurs as a normal constituent of feces and uroporphyrin is found in minute amounts in normal urine. The exact site and mode of secretion of porphyrins is still in doubt but it is thought that the most important organ of excretion is the liver.

Acute porphyria is a disease of disturbed pigment metabolism. It is characterized by abdominal pain, nervous and mental symptoms, and the excretion of large amounts of porphyrins in the urine. It is a familial disease usually inherited as a Mendelian dominant characteristic and is found more commonly in females than in males.

The porphyrins produce spasticity of smooth muscle and degenerative changes in the autonomic ganglia; they are found as intracellular pigment

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deposits as well as in large quantities in the urine. The symptoms depend upon the extent and degree of pathologic involvement. The diagnosis is made by the identification of porphyrins in the urine. There is no specific treatment and the disease usually terminates fatally. Acute porphyria may be diagnosed by the identification of porphobilinogen in the urine according to the method of Watson and Schwartz.[1]

Case Report

Miss J. M., aged 20 years, first came to our attention in 1953. Her past medical history included several admissions to Reading hospitals. In 1942, the diagnosis of chronic endocarditis was made and in 1943 the diagnosis was confirmed in association with recurrent rheumatic fever. She was hospitalized again in 1950 with the same diagnosis. In 1952 she was operated upon for "subacute appendicitis" but she was not relieved of her pain.

In 1953, she was first admitted to the medical service of Community General Hospital because of marked weight loss and a history of red to almost black urine for a year.

The significant laboratory findings were as follows: hemoglobin 9 Gm., or 58 per cent; red blood cell count 3.29 million; white blood cell count 6,650; and normal differential counts. Blood urea nitrogen determinations ranged from 24.5 to 75 mg. per cent, the average being 50.7 mg. per cent; nonprotein nitrogen determinations ranged between 74 and 86 mg. per cent, the average being 80 mg. per cent. Urinalysis was negative except for occasional red blood cells and white blood cells. Urea clearance was between 19 and 25 per cent of normal clearance. Fishberg concentration tests showed the specific gravities to be 1.013, 1.022, 1.020.

The diagnosis on discharge was now rheumatic heart disease and acute exacerbation of chronic glomerulonephritis.

In the outpatient department she was studied by Dr. Harold Farber who made the diagnosis of acute intermittent porphyria. Urine specimens were now found to be positive for porphobilinogen. The presence of this pigment in the urine is pathognomonic of acute intermittent porphyria.

She was given supportive treatment but discontinued her outpatient visits until she reported to the obstetric clinic for care on Aug. 12, 1953. She was immediately admitted to the hospital for re-evaluation. On admission, she complained of redness of the urine, fainting attacks for two weeks, numbness in the right foot during the preceding three days, sense of bitemporal pressure, and dizziness on motion.

Her pregnancy on the day of admission was of about 18 weeks' duration. Physical examination revealed the blood pressure to be 120/80 and examination of the abdomen revealed the uterus to be enlarged to a size consistent with the given length of gestation.

Laboratory studies were repeated and the following are the average results of the many tests done: hemoglobin 6.5 Gm., or 43 per cent; red blood cell count 3.35 million; white and differential counts normal; blood urea nitrogen 25.5 mg. per cent; nonprotein nitrogen 36 mg. per cent; urea clearance 31.5 per cent; phenolsulfonphthalein 50 per cent excretion in the three specimens; specific gravities by the Fishberg concentration test were: 1.020, 1.018, 1.018, 1.025, 1.024, 1.027.

The patient was first seen by one of us (L. R.) one week after admission. She was then in good condition, but laboratory study had revealed impaired kidney function both before and during her pregnancy and immediate termination of the pregnancy was recommended.

During the following week, the patient became progressively worse. She received 1,000 c.c. of blood and was operated upon under spinal anesthesia, a hysterotomy and Pomeroy sterilization being performed. The fetus weighed 500 grams and measured 26 cm.

Postoperatively, the blood urea nitrogen rose to 49 mg. per cent and the blood pressure rose to 160/100 on the second postoperative day. Following this, blood urea nitrogen and blood pressure tended to return to the preoperative levels.

Postoperative treatment consisted of repeated blood chemistry determinations and electrolyte balance. She received 20 per cent glucose in distilled water, in saline, or in molar lactate as was indicated by laboratory determinations. Blood transfusions were given as often as anemia or reduced blood protein indicated their need. On the third and fourth postoperative days, the patient was able to take advantage of her bathroom privileges but on the fifth day, she had such weakness of the legs that she was unable to leave her bed.

There had been no preoperative eye ground examination, but postoperatively the eye grounds revealed no elevation of the discs. The light streak was increased and there were extensive retinal hemorrhages. She developed facial edema after which her condition grew progressively worse and she died on the sixteenth postoperative day. The wound had healed. The cause of death was acute respiratory paralysis.

An autopsy was performed. The pertinent findings were:

Heart.—There was fusion of the cusps of the mitral valve and the valve leaflets were somewhat rigid. There was roughening of the endocardium.

Liver.—Weighed 1,800 grams, was somewhat enlarged, and contained a number of yellowish macules throughout.

Kidneys.—The left kidney weighed 140 grams, the right 130 grams. The capsule of each stripped easily. The parenchyma was slightly widened and pale. There were no important gross changes in either kidney.

Histologic Examination.—

Kidney: Showed a very intense degree of cloudy swelling with necrosis and actual degeneration of the tubules. The glomeruli were well filled with blood but showed proliferation of the capsular epithelium and hyalinization of the capsular membrane. This epithelial proliferation was seen as single, swollen cells or small islands of cells without reduplication. There was also dilatation and hyalinization of the afferent arterioles at their point of entrance into the glomerulus and marked hyalinization of numerous arterioles at points distal to the glomerulus. No glomeruli were hyalinized and all appeared to be completely or partially filled with blood except for occasional loops.

Liver: Showed dilated sinusoids in some areas, marked cloudy swelling with cytoplasmic granulation and fragmentation of the parenchymal cells, and areas of complete disintegration of the parenchyma, with only vague outlines of cells and pale nuclei remaining. Other areas showed focal hemorrhages.

Summary

1. Detailed study of a patient 20 years of age with acute intermittent porphyria complicated by pregnancy is herein reported.

2. Repeated studies of kidney function prior to and during pregnancy indicated impairment.

3. Because of persistent evidence of impaired kidney function, pregnancy was terminated.

4. Postoperative management consisted of maintenance of electrolyte balance, blood transfusions, and symptomatic treatment.

Conclusion

The management of such patients depends upon the status of kidney function and the period of gestation.

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A SOURCE OF ERROR IN THE ANTENATAL DIAGNOSIS OF ERYTHROBLASTOSIS

The Importance of Performing Antibody Tests Early in Pregnancy

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THE Rh-Hr types and their application in clinical medicine have been the subject of a recent survey.[1] The purpose of this paper is to point out the importance of performing a test for Rh antibodies in the Rh-negative woman as soon as she becomes pregnant. This base-line titration performed at the beginning of each pregnancy, even the first pregnancy, is of value for comparison with titers obtained near term.

Not enough emphasis has been placed on the value of early Rh antibody tests on the blood of Rh-negative women who are pregnant for the first time. Probably most physicians have been lulled into a false sense of security, because erythroblastosis is rarely observed in the first-born children of Rh-negative women. Severe erythroblastosis can occur, however, in babies of Rh-negative primiparas who have been sensitized by transfusions of blood or plasma received before marriage, especially transfusions given before the discovery of the Rh factor. The importance of early Rh antibody titrations is twofold: first, it will be helpful in predicting the probable outcome of a given pregnancy, and, second, the doctor will be saved the embarrassment of parental recriminations and the possibility of a lawsuit.

Recently, the following case was referred to me in which failure to carry out early Rh antibody titrations led to an incorrect forecast of erythroblastosis in the baby.

Case Report

J. K., 24 years of age, was 8 months pregnant when first seen, with a history of having received several blood transfusions when she was 7 years old. She had received no other blood or plasma transfusions since then. This was her first pregnancy. Her obstetrician referred her to me because she had been found to be Rh negative and sensitized to the Rh factor, and her Rh antibody titer appeared to be rising. When she was 6 months pregnant, her blood was reported to have an Rh antibody titer of 128 units by the albumin-plasma conglutination method. One month later, another laboratory reported a titer of 128 units by the antiglobulin method, and the same titer for enzyme-treated cells. About 6 weeks before term the original laboratory reported a titer of 512 units by the albumin-plasma conglutination method. At this point, the patient, who had now completed her eighth month, and her husband were sent to me.

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The blood grouping and Rh-Hr tests on the prospective parents gave the following results:

BLOOD OF	GROUP	Rh-Hr TYPE
Expectant father	A_1	Rh_1rh
Expectant mother	O	rh

It will be seen that the patient is Rh negative and her husband Rh positive and presumably heterozygous.

Tests for Rh antibodies were carried out on the patient's serum and gave the following results:

Agglutination method—negative
Albumin-plasma conglutination method—positive, 64 units
Antiglobulin method—positive, 184 units
Enzyme-treated cells—positive, 240 units

These results reveal a strong sensitization to the Rh factor.

A week later the Rh antibody tests were repeated and yielded the following results:

Agglutination method—negative
Blocking test—positive, 1½ units
Albumin-plasma conglutination method—positive, 44 units
Antiglobulin method—positive, 400 units
Enzyme-treated cells—positive, 400 units

These titers are not significantly different from the previous results, and again show a strong Rh sensitization.

In view of the difference of the A-B-O groups in the prospective parents, the alpha and beta antibodies of the patient's serum were titrated with the following results:

Agglutination method: Anti-A (for A_2 cells)—5 units, Anti-B—5 units
Acacia conglutination method: Anti-A (for A_2 cells)—30 units, Anti-B—5 units

These titers are low and of no clinical importance.

With regard to the probable outcome of the pregnancy we reasoned that, since the husband was probably heterozygous, there was approximately a 50 per cent chance of the baby's being Rh negative, in which case the maternal antibodies could not harm him. In such an event the Rh antibodies in this patient's serum would have to be a carry-over from her sensitization by the transfusions received 17 years previously. After such a long period of time, however, one would expect the titers to be considerably lower, since the tendency of the antibody titer is to drop gradually, unless the individual is restimulated by an injection of Rh-positive blood or a pregnancy with an Rh-positive fetus. Therefore, based on past experience in cases of this nature, we postulated that the patient was probably carrying an Rh-positive fetus and that leakage of fetal blood early in the pregnancy had caused the antibody titer to rise to its present high level. As no antibody titer had been done before the sixth month of pregnancy, we had no way of checking this hypothesis. On the other hand, if the fetus were Rh positive with such a high maternal Rh antibody titer, one might expect some indication of fetal distress or death, and on this basis an Rh-negative fetus would appear to be a more likely possibility. Weighing one probability against the other, we felt that the safer assumption was that the fetus was Rh positive and severely affected, and we proceeded on this basis.

For the reasons just given, it was decided to deliver the baby vaginally, by inducing labor two weeks before term. When conservative measures, including Pituitrin drip and rupture of the membranes, failed, however, there was no alternative left but to perform a cesarean section. A normal-appearing baby girl, weighing 6 pounds, 9 ounces, was delivered. There was no evidence of anemia or jaundice one hour after birth. The direct

antiglobulin test was negative, and this was explained when the baby proved to be Rh negative. Examination of the cord blood revealed a hemoglobin concentration of 18 Gm., an icterus index of 16 units, and the following Rh antibody titers:

Agglutination method—negative
Blocking test—positive, 1 unit
Albumin-plasma conglutination method—positive, 48 units
Antiglobulin method—positive, 160 units
Enzyme-treated cells—positive, 500 units

Thus, it is evident that the antibody titers of the baby's serum are equal to those of the maternal antibody titers, as is to be expected.

Comment

This case demonstrates how failure to carry out Rh antibody titers early in pregnancy led to a misinterpretation of the findings obtained late in pregnancy. It may seem difficult to accept the presence of a high titer of antibodies after the passage of as long a period as 17 years after the last exposure to the Rh antigen. The high titer in the present case cannot be attributed to a nonspecific anamnestic rise, caused by an Rh-negative fetus, since, as Wiener and associates[2] have shown, neither the injection of Rh-negative blood nor pregnancies with Rh-negative fetuses cause a rise in Rh antibody titer. Reports in the literature claiming nonspecific anamnestic rises in Rh antibody titers are due either to errors in technique or to misinterpretation of the results in antibody titrations, which have a large intrinsic error. Presumably, this patient was so extremely immunized by the transfusions she received that, despite the decline in titer to be expected with time, even after 17 years the values were still considerably elevated. The main point, however, is that, had an antibody titer been performed at the beginning of the pregnancy, there would have been no difficulty in interpreting the findings.

Summary and Conclusions

An unusual case is reported of a primipara who was strongly sensitized to the Rh factor by blood transfusions received 17 years before her first pregnancy, and who retained a very high titer even after the passage of so many years. This woman gave birth to a normal Rh-negative baby.

It is pointed out that, if the Rh antibody titers are done early in pregnancy, as well as late in pregnancy, and by the same person, the latter will be better equipped to predict the probable outcome of a given pregnancy. It is urged, therefore, that all Rh-negative women have tests for Rh antibodies performed as early in the pregnancy as possible, especially when it is known that they have received blood transfusions before marriage.

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COMBINED INTRA- AND EXTRAUTERINE PREGNANCY

A Case Report

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THE occurrence of simultaneous intrauterine and extrauterine pregnancy is relatively rare. Ludwig[1] collected a total of 353 cases through 1938. DeVoe and Pratt[2] found 69 cases reported in the literature between 1935 and 1947, and calculated the expected incidence of combined pregnancy as about 0.003 per cent of all pregnancies.

In the case being reported triplets were present, the tubal pregnancy being a twin pregnancy. This situation is not particularly unusual in combined pregnancy. Neugebauer[3] drew attention to the fact that a considerable number of combined pregnancies are of the triplet variety, with either twin fetuses in a tube and a single fetus in the uterus, or twin fetuses in the uterus and a single fetus in the tube.

The chief problem presented by combined pregnancy is that of diagnosis. If rupture of the ectopic pregnancy occurs early in the course of the pregnancy, the presence of an associated intrauterine pregnancy may easily be missed. Frequently the intrauterine pregnancy is not recognized even at the time of operation since it is known that a certain degree of uterine enlargement occurs in ectopic pregnancy alone. If rupture of the ectopic pregnancy occurs after there is enough uterine enlargement to indicate the presence of an intrauterine pregnancy, the tendency is to ascribe the symptoms to some associated condition such as twisted ovarian cyst or appendicitis complicating pregnancy. Novak[4] says that, if there is definite uterine enlargement in a case otherwise suggesting ectopic pregnancy, the diagnosis of combined pregnancy should be entertained. This is particularly true if there is no uterine bleeding. If profuse vaginal bleeding occurs in a case otherwise suggesting ectopic pregnancy, the diagnosis of abortion of an intrauterine pregnancy and rupture of a combined ectopic pregnancy should be considered.

Case Report

Q. S., a 31-year-old Negro woman, was admitted to Chester Hospital on June 19, 1951. On admission, she complained of abdominal pain of one day's duration. She was in the third month of her third pregnancy, which had been progressing uneventfully. On the day of admission she noticed generalized abdominal pain accompanied by nausea and vomiting. She was believed to be having a threatened abortion and was admitted to the hospital. She was observed for two days during which time no vaginal bleeding occurred. On June 21, 1951, the pain localized in the right lower quadrant of the abdomen. At this

time a surgical consultation was requested. A diagnosis of appendicitis complicating pregnancy was made and laparotomy was carried out on the evening of June 21, 1951.

Examination at the time of consultation revealed an acutely ill young woman. Her temperature was 99° F., pulse 100. Positive findings were limited to the abdomen and pelvis. The abdomen was slightly distended, and there was extreme tenderness over McBurney's point without much muscle guarding. There was no vaginal bleeding. The cervix was soft, and the uterus was enlarged to the size of a three months' pregnancy. No adnexal mass could be felt. Bimanual pressure elicited tenderness in the right lower abdominal quadrant, but this was not thought to represent adnexal tenderness.

There was a leukocytosis of 15,600 with a differential count of 87 per cent polymorphonuclear neutrophils and 13 per cent lymphocytes. The erythrocyte count was 3.56 million with 9.5 Gm. hemoglobin.

X-ray of the abdomen revealed a soft-tissue density in the pelvic basin probably representing an enlarged uterus.

Operative Procedure.—Under general anesthesia a right McBurney incision was made. When the peritoneum was opened, clotted blood was noted immediately. Accordingly, in the belief that an ectopic pregnancy was present, the incision was extended downward and medially, opening the rectus sheath, securing, ligating, and dividing the deep epigastric vessels and transecting the outer third of the right rectus muscle. On exploration, the right Fallopian tube was seen to be distended. Rupture of the tube had occurred, but there was not an excessive amount of blood in the abdomen. The tube was clamped and amputated, the stump being ligated. Upon examination of the removed tube, twin fetuses were found to be protruding through a rent in the wall. The uterus was about the size of a three months' pregnancy and had the soft consistency typical of pregnancy. It was believed to contain another fetus as the enlargement was much greater than that which occurs only with ectopic pregnancy. The appendix was examined but was not disturbed. The left tube was palpated and was apparently normal. The abdomen was then closed in layers. Vaginal bleeding was noted at the conclusion of the operation.

Postoperative Course.—On June 22, 1951, the day following operation, the patient had a slight vaginal bleeding. A transfusion of 500 c.c. of whole blood was given. Bleeding was also noted on June 23, but ceased on the next day. She was allowed out of bed on June 28, 1951, the seventh postoperative day, at which time the skin sutures were removed. She was discharged on the following day having made a good recovery.

Following discharge from the hospital, the patient continued under the care of her obstetrician. In July she noticed fetal movement for the first time. The pregnancy progressed without incident under routine prenatal care. On Dec. 28, 1951, she went into labor and was delivered of a normal female infant by the vaginal route.

Comment

This case illustrates the problem of diagnosis presented by combined pregnancy when the intrauterine pregnancy has progressed to the stage of definite uterine enlargement at the time of rupture of the ectopic pregnancy. Appendicitis seemed the most likely possibility because of the physical and laboratory findings. The signs and symptoms were not entirely typical of appendicitis, however, and it is in such cases that the possibility of combined pregnancy should not be overlooked.

As in this case, it is often possible in combined pregnancy to carry the intrauterine pregnancy to term. If there is no interference with the intrauterine pregnancy at the time of discovery and treatment of the ectopic pregnancy, the chances of obtaining a live baby are good. DeVoe and Pratt[2] reported the survival of 29 intrauterine fetuses in a possible 44 cases (65.9 per cent).

Summary

A case of twin tubal pregnancy and intrauterine pregnancy is reported. The associated ectopic pregnancy was not recognized until the time of operation. The intrauterine pregnancy progressed to term with the delivery of a healthy infant.

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PREGNANCY COMPLICATED BY SUBARACHNOID HEMORRHAGE FOLLOWING ANTICOAGULANT THERAPY OF SUBACUTE BACTERIAL ENDOCARDITIS

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SUBARACHNOID hemorrhage has been regarded as a rather rare complication of pregnancy, and, prior to the use of antibiotics, subacute bacterial endocarditis was very seldom found complicating pregnancy. To see a case of pregnancy in which both of these complications occur is exceedingly uncommon, and, for this reason, it is felt that the following case is of sufficient interest and rarity to make it worthy of reporting in some detail.

Case Report

The patient, a 22-year-old gravida i, para 0, was first admitted to Scripps Memorial Hospital on July 18, 1952, because of complaints of marked fatigue, dyspnea, and orthopnea. Two days prior to admission her family physician had noted that the liver edge was 4 cm. below the right costal margin, and that she had small red petechial spots on both hands. The sedimentation rate prior to admission was 53 mm. per hour and a blood culture had shown a short-chain streptococcus which proved to be sensitive to Aureomycin, Terramycin, and penicillin. Her last menstrual period had begun on Nov. 14, 1951, and she had been under the care of her family physician since March 14, 1952, at which time he had found that she was approximately four months pregnant, had an enlarged heart by clinical and fluoroscopic examination, and had loud systolic murmurs over the aortic and mitral areas. An electrocardiogram on March 14, 1952, showed a normal tracing.

Her past history was significant in that she had had rheumatic fever in 1941, and had been successfully treated for subacute bacterial endocarditis with massive doses of penicillin for 3 months in 1949.

A consultant in internal medicine saw the patient on the day of her hospital admission and confirmed the diagnosis of subacute bacterial endocarditis. He recommended continuing the present therapy (2,000,000 units of penicillin daily) and also recommended administration of an anticoagulant to prevent any further embolic episodes.

The patient was given 200 mg. of Cumopyran* on July 21, 1952 (on which date the prothrombin time was 77 per cent) and was maintained on a dose of 25 mg. daily. Her general condition seemed to improve while she was in the hospital and her husband, against the advice of the family physician, took her home on July 26, 1952, at which time the prothrombin time was 20 per cent. Very shortly after she returned home she developed dizziness, headaches, and became very restless and started vomiting. During that night she developed diplopia and had a small emesis of coffeeground material. Her doctor gave her large doses of vitamin K intravenously and discontinued the Cumopyran but she became progressively worse. Finally the family physician was able to convince the husband that the patient should again be hospitalized, and at 8:15 P.M. on July 31, 1952, she was readmitted to Scripps Memorial Hospital.

*Cyclocumarol, Abbott.

The medical consultant again saw the patient on the day of her hospital readmission and found that she had grossly bloody spinal fluid which was xanthochromic on centrifuging. It was his impression at the time that the patient was suffering from a subarachnoid hemorrhage, subacute bacterial endocarditis, and rheumatic heart disease. Her condition became progressively worse despite large doses of vitamin K, blood transfusions, sedation, continuation of the penicillin therapy, and daily prothrombin checks. On Aug. 2, 1952, she began having moderately strong uterine contractions without making any progress, and I was asked to see the patient in consultation regarding her obstetrical status. At that time the head was high in the pelvis, the cervix was not effaced and was only 1 cm. dilated. The uterus was approximately term size and the fetal heart tones were normal. Vaginal delivery as soon as the cervix was fully dilated and the head below the spines was recommended; cesarean section was advised only in case the patient failed to make normal progress in labor. Fairly strong contractions continued but the patient made no progress, and after fifteen hours of labor she showed definite signs of becoming weaker and was semicomatose. She was then taken to the operating room and a low cervical cesarean section with bilateral tubal ligation was performed at 8:25 P.M. on Aug. 3, 1952. The total operating time was 35 minutes and, interestingly enough, it was not necessary to ligate one single blood vessel anywhere in the abdominal incision. A 6 pound, 15 ounce male infant was delivered from the left occipitoanterior position and cried almost immediately. The baby did very well while in the hospital, showing no signs of hemorrhagic tendencies at any time, and was discharged 3 weeks later in excellent condition. The tubal ligation was done because it was felt that it would add very little to the operating time, and, if the patient should recover from her present illness, she should certainly never become pregnant again. The type of anesthetic to be given was thoroughly discussed with the anesthetist, who was an experienced and well-trained anesthesiologist, and it was his feeling that the patient should be given a spinal anesthetic, even in the presence of grossly bloody spinal fluid, rather than a local or a general anesthetic, as she seemed to be on the verge of convulsions at the slightest stimulation. She seemed no worse when she was returned to her room immediately after surgery, but continued to become gradually weaker and died at 4 P.M. on Aug. 4, 1952.

Pertinent laboratory findings were as follows: July 31, 1952, hemoglobin 9 Gm., red blood count 3.15 million, white blood count 15,600 with 89 per cent polymorphonuclear leukocytes. The blood was type AB, Rh positive, serology negative. The prothrombin time on Aug. 1, 1952, was 85 per cent and again on August 2, it was 85 per cent. Urinalysis Aug. 2, 1952, was normal. Blood count done on the morning of Aug. 4, 1952, showed the hemoglobin to be 12.6 Gm. with the red blood count 5.56 million (some of this increase was probably due to hemoconcentration).

Autopsy, performed by Dr. T. A. Le Strange, revealed the following conditions: (1) diffuse subarachnoid hemorrhage with no definite point of origin; (2) extradural hematoma around the base of the sella turcica, appearing to originate in the cavernous sinus; (3) subacute bacterial endocarditis with mitral vegetation; (4) rheumatic valvulitis and rheumatic myocarditis; (5) aortic and mitral valvular insufficiency; (6) cardiac hypertrophy; (7) bronchopneumonia; (8) marked chronic passive congestion of the lungs, liver, and kidneys; (9) postpartum uterus with recent cesarean section incision and bilateral tubal ligation; (10) multiple splenic infarcts; (11) splenomegaly.

Review of the Literature

The first case of pregnancy complicated by subarachnoid hemorrhage was reported by Gerin-Rose[1] in 1859, and relatively few cases have been reported in the ninety-five years since that time. In September, 1951, Schwartz[2] reported that a review of the world's literature to date revealed only 29 cases of pregnancy complicated by subarachnoid hemorrhage, with mortality rates in the various component series ranging from 28 per cent to 50 per cent, and he added 3 new cases of his own, all of which patients died. In the following

month Conley and Rand[3] reported 8 new cases of subarachnoid hemorrhage complicating pregnancy (six lived and two died) and in their bibliography they included reports of 13 cases of subarachnoid hemorrhage in pregnancy or in the immediate postpartum state (six of these lived and seven died) which were not included in Schwartz's list of references. Since then, reports of pregnancy complicated by subarachnoid hemorrhage have been published by Trodella[4] (one case, patient survived), Johnson[5] (four cases, all survived), and Decker and Rowe[6] (one case, patient survived). These cases, plus the present one, make a total of 60 cases of pregnancy complicated by the occurrence of subarachnoid hemorrhage reported in the world's literature to the present time.

In none of the previously reported cases was there any mention made of previous treatment with anticoagulant drugs, so that this case, to the best of my knowledge, is the first reported case of pregnancy complicated by subarachnoid hemorrhage following anticoagulant therapy for subacute bacterial endocarditis. For further discussion of the etiology, prognosis, diagnosis, and treatment of subarachnoid hemorrhage the reader is referred to the excellent articles by Schwartz[2] or Conley and Rand,[3] or to any standard textbook of neurology. Most authors recommend vaginal delivery, if possible, but Conley and Rand[3] advocate delivery by cesarean section in all cases of pregnancy complicated by subarachnoid hemorrhage to avoid any straining by the patient during labor.

Pedowitz and Hellman[7] have recently published a summary of 120 cases of subacute bacterial endocarditis preceding or complicating pregnancy. Their series included 113 cases (12 of which had been previously reported in the American literature) from 102 American hospitals and 7 cases which were collected from the British literature. One hundred two cases went to viability with the loss of 3 infants, a viable fetal loss of 2.9 per cent. There were 3 maternal deaths in the healed group with a maternal mortality rate of 3.5 per cent, while the rate rose to 14.2 per cent when subacute bacterial endocarditis occurred during pregnancy. The maternal mortality rate for the entire series was 6.6 per cent. They concluded that pregnancy is contraindicated for the first six months following clinical cure of subacute bacterial endocarditis and recommended therapeutic abortion if pregnancy occurred in this period. They did not believe that healed subacute bacterial endocarditis of longer duration was any contraindication to pregnancy, however, nor did they think that pregnancy predisposed to the recurrence of the endocarditis. They recommended that the prenatal care and conduct of labor should be similar to that given any patient with heart disease, and that cesarean section be performed only for obstetrical indications. They also advocated routine intra- and postpartum use of antibiotics in all patients with heart disease to prevent the occurrence or recurrence of subacute bacterial endocarditis, and it was their impression that the treatment of subacute bacterial endocarditis is as successful in the pregnant as in the nonpregnant cardiac patient.

Flaxman[8] has reported 32 deaths from Dicumarol therapy. He found that this was the commonest cause of fatalities resulting from drugs given orally. Nine of the fatalities in his series occurred even with careful laboratory controls.

Summary

A case of pregnancy complicated by subarachnoid hemorrhage following anticoagulant therapy for subacute bacterial endocarditis is presented. A normal living infant was delivered by cesarean section following failure of progress after fifteen hours of labor. The infant survived but the mother succumbed.

Fifty-nine cases of subarachnoid hemorrhage complicating pregnancy have been previously reported, but, to the best of my knowledge, this is the first reported case of pregnancy in which the occurrence of subarachnoid hemorrhage was preceded by subacute bacterial endocarditis treated with an anticoagulant drug.

Current concepts regarding the management of pregnancy complicated by subarachnoid hemorrhage or by subacute bacterial endocarditis are reviewed.

Extreme caution and very careful supervision of the patient are imperative whenever anticoagulants are used in the treatment of any condition, as these drugs have been shown to have very high lethal potentialities.

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LEUKEMIA AND PREGNANCY

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LEUKEMIA associated with pregnancy is an infrequent complication. One-hundred eighteen cases[1-13] have been found reported in the literature. We wish to add two more.

Case 1.—Mrs. L. F. P., a 40-year-old white woman, gravida i, para i, had been under treatment for chronic myelogenous leukemia for two years prior to conception. The white blood cell count at that time was 49,450 with 2 basophils, 1 eosinophil, 8 myelocytes, 28 young forms, 27 band forms, 24 segmented forms, 4 lymphocytes, and 4 monocytes. Three and a half months later the total white blood count was 101,300. Under Urethane treatment the count dropped to 8,750. At approximately six to eight weeks of undiagnosed pregnancy the white count rose to 81,800. At this time she was given radiophosphorus.

Throughout the illness the patient was erratic about her treatment and was not seen again by a physician until approximately the thirty-fourth week of gestation. She was admitted to the hospital on Jan. 12, 1951, stating that her last normal menstrual period was on May 20, 1950. Three months before the patient was seen she began having intermittent edema of the lower limbs which for the past four weeks had increased in severity and persisted all the time. Blood pressure was 160/110; pulse 96. Urinalysis showed 20 mg. of albumin per 100 c.c. Marked edema was present to the knees. There had been an 8 pound weight loss, part of which may have been due to nausea and vomiting which had persisted throughout the pregnancy. The leukocyte count was 6,250 with 5 band forms, 83 segmented forms, 11 lymphocytes, and 1 monocyte. Hemoglobin was 9 Gm. per 100 c.c. Blood chemistry was within normal limits except for a decrease in the total proteins to 4.59 Gm. per cent.

Complete bed rest and sedation resulted in a lowering of the blood pressure to 140/90 and a weight loss of 9 pounds within 24 hours. The blood pressure remained unstable, however, and intermittently returned to previous heights. Urinalysis was negative after the initial examination. On the sixth day in the hospital medical induction was started with the fetal head at minus 4 station, the cervix partially effaced, and no dilatation. On the third attempt at induction the patient went into active labor and the membranes ruptured spontaneously. With the start of labor, 150 mg. of protamine sulfate and 10 mg. of toluidine blue were given by intravenous drip as a preventive measure against hemorrhage.

On Jan. 21, 1951, after a fifteen-hour labor, the patient was delivered spontaneously of a 3 pound, 12 ounce, stillborn, macerated female infant. Blood loss was minimal and the third stage uneventful. Three and a half hours later there suddenly developed an increased amount of bleeding from a firm uterus with the development of shock. A transfusion of 1,000 c.c. of whole blood was given, followed by additional intravenous fluid containing protamine sulfate and toluidine blue. The flow decreased to an average postpartum amount, and the remainder of the postpartum period was uneventful. The leukocyte count after delivery was 19,550.

Following discharge from the hospital she was treated with blood transfusions and P^{32}. She was very irregular in returning for follow-up treatments. The leukocyte counts were in the 200,000 to 300,000 range. She was not seen in the clinic from July 3, 1951,

until Feb. 28, 1952, at which time the white count was 246,000 and hemoglobin 6.7 Gm. per cent. Symptoms of weakness, lassitude, and bruising were present. She was hospitalized in March, 1952, and again in July, 1952. In July she was placed on triethylenemelamine without favorable response. She died July 27, 1952, 18 months and 6 days following delivery. The total length of the disease was 4 years and 2 months.

CASE 2.—Mrs. O. S. was a 33-year-old gravida iv, para iii, white woman, who was delivered of her other pregnancies without difficulty. The babies all averaged about 8 pounds. Her last normal menstrual period was May 5, 1952. The expected date of delivery was Feb. 12, 1953. Her menstrual history was normal, and there had been no change in the characteristics of her periods. Her weight was 94 pounds and blood pressure 98/60 at the time of her first clinic visit. There was a history of symptoms compatible with leukemia for 17 months and a diagnosis of chronic myelogenous leukemia for 12 months. Blood studies done two months before the onset of the pregnancy showed 386,000 white blood cells with a differential count of basophils 3; eosinophils 1; myelocytes 35; young forms 23; band forms 28; segmented forms 9; lymphocytes 1; monocytes 1.

The prenatal course of the patient was characterized by several hospital admissions and multiple blood transfusions. At 24 weeks' gestation the spleen was noted to be enlarged and to extend down to the umbilicus. The liver at this time was palpable to four fingerbreadths below the costal margin. Ulcerations were present in the mouth. At 35 weeks' gestation there were bilateral enlarged and tender inguinal glands. Blood pressure and weight gain had been normal.

The patient was admitted to the hospital on Jan. 25, 1953, in labor, and was delivered spontaneously from a cephalic presentation of a viable male infant that weighed 4½ pounds. There was an estimated blood loss of 250 c.c. following delivery. The patient was given Ergotrate and Pitocin following delivery. No other medication was necessary for bleeding. On the twelfth postpartum day, however, she developed diarrhea and excess vaginal bleeding. This was treated with multiple blood transfusions, toluidine blue, protamine sulfate, and vitamin K. She was discharged from the hospital in immediate satisfactory condition.

The patient moved out of state and died 16 months after the diagnosis of chronic myelogenous leukemia had been made, 21 months from the beginning of her symptoms, and 4 months after the conclusion of her pregnancy.

Of the 120 cases of leukemia reported, 43 have been of the acute type, 76 of the chronic type, and 1 unclassified. The myelogenous form of the disease is the most common in both acute and chronic leukemia, 55.6 per cent of the acute and 92.1 per cent of the chronic forms being of the myelogenous type.

Of the 114 cases in which the information is available, in 68.2 per cent of the chronic cases the onset was prior to pregnancy, while in only 14.3 per cent of the acute cases the onset was before pregnancy.

The age and the parity of the patients did not seem to be related to the disease, as they varied from gravida i to para viii and from 15 years to 40 years of age.

In the 101 cases in which the information is available, 40.6 per cent of those with acute cases and 20.3 per cent of those with chronic cases were delivered or died undelivered before the third trimester.

Information concerning fetal mortality in relation to the length of pregnancy is available in 36 of the 43 acute cases and in 47 of the 76 chronic cases. In the acute cases 63.9 per cent of the infants were lost. In 39.13 per cent of the pregnancies which progressed past seven months the infants were lost. The outlook for survival of the infant in the chronic cases was better, with a total loss of 38.3 per cent and a loss of 14.9 of the infants past 7 months' gestation.

Shub, Black, and Speer[13] have shown that pregnancy had a deleterious effect on the course of the disease in a patient with chronic myelogenous leu-

kemia. They have shown that the mean length of survival in cases of chronic myelogenous leukemia associated with pregnancy is 29.7 months, and in those cases in which the disease has been present for one year or less the mean length of survival is 15.6 months. This is a decrease in the time of survival by 9.9 months and 24 months as compared to the mean survival rate of 39.6 months in chronic myelogenous leukemia uncomplicated by pregnancy, as studied by Shimkin, Mettier, and Bierman.[14]

Of those with acute cases 75.7 per cent died during pregnancy or within two weeks after delivery. Only 12.1 per cent of those with chronic cases died within this period.

Either immediate or late postpartum hemorrhage or an excess flow over several postpartum days necessitating blood replacement occurred in 18 cases, or 22.8 per cent of the 79 cases in which the information is available. The frequency of bleeding in the acute and chronic cases was 18.9 per cent and 25.0 per cent, respectively.

No cases have been reported in which the disease has been transmitted to the infant.

Summary

1. Two additional cases of chronic myelogenous leukemia complicated by pregnancy are reported.

2. A brief review of the available data on 120 cases of leukemia associated with pregnancy is presented.

3. Pregnancy probably shortens the total life expectancy of the patient with leukemia.

4. As strict a medical control as possible of the leukemia and associated anemia should be maintained in an endeavor to carry the pregnancy to the point of viability, as most infants are lost before the seventh month.

5. Pregnancy should be avoided in patients with leukemia.

6. Operative intervention is probably not indicated except for obstetrical reasons.

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UMBILICAL ENDOMETRIOSIS

A Case Report

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ENDOMETRIOSIS of the umbilicus is uncommon, and when discovered usually provokes considerable discussion, particularly as to etiology. Survey of the literature reveals that since Villar first described this condition in 1886 about 108 cases have been reported.

During the two menses preceding hospitalization, this 48-year-old white woman had experienced for the first time in her life some soreness of the umbilicus accompanied by a slight bloody discharge. This soreness and bleeding began and ended with the menstrual periods.

Previous menses had always been normal and regular with no dysmenorrhea. There had been one normal pregnancy 12 years before. She had always been healthy and active and other past history was without significance.

With the first episode the family physician cauterized the bleeding point of the umbilicus and on examination found a small pelvic mass. The second episode brought the patient to the hospital, at which time the positive physical findings were limited to the umbilicus and the pelvis.

The umbilicus was slightly enlarged, definitely darker in color and of increased firmness. Pelvic examination revealed a tender mass 5 cm. in diameter, in the right adnexa. The uterus was slightly irregular and was thought to contain fibroids.

A bilateral salpingo-oophorectomy and hysterectomy were performed for fibromyomas of the uterus and endometriosis. There was extensive endometriosis involving the myometrium, the tubes, and ovaries, with a chocolate cyst, 5 cm. in diameter, of the right ovary. A small dermoid cyst, 1 cm. in diameter, of the left ovary was also present.

The umbilicus was removed intact and on section revealed several small cystic structures containing a dark, coffee-ground type of material.

Microscopic examination of the tissues confirmed the diagnosis of pelvic endometriosis. Beneath the skin of the umbilicus there was a great deal of old hemorrhage, as well as numerous endometrium-like glands. These glands were surrounded by a well-defined dense cytogenic stroma characteristic of endometrial stroma; some of the glands contained old blood (Fig. 1).

Comment

Endometriosis is defined by Novak[1] as "the condition in which tissue resembling endometrium more or less perfectly is found aberrantly in various locations." An anatomical differentiation is made by some authors between internal endometriosis (adenomyosis) and external endometriosis. The former extends diffusely throughout the uterine wall, whereas the latter type is found on or near the peritoneal surface of the uterus, ovaries, pelvis, or elsewhere in the body. Isolated endometrial tissue, surrounded by endometrial stroma or smooth muscle, may be called an endometrioma.

Endometriosis occurs during the sexually active period of life, starting after puberty and stopping in most instances at the menopause.[1] Most often it is found in the fourth and fifth decades.

Ectopic endometrium does not always participate in menstruation; frequently the intermenstrual cyclic changes are absent, the tissue being unable to respond to hormones.[4]

There are at least seven different theories concerning the pathogenesis of endometriosis; they are: (1) direct myometrial extension; (2) congenital theories; (3) serosal metaplasia; (4) implantation theory; (5) lymphatic metastasis; (6) hematogenous metastasis; (7) analogy to endometrial carcinoma.

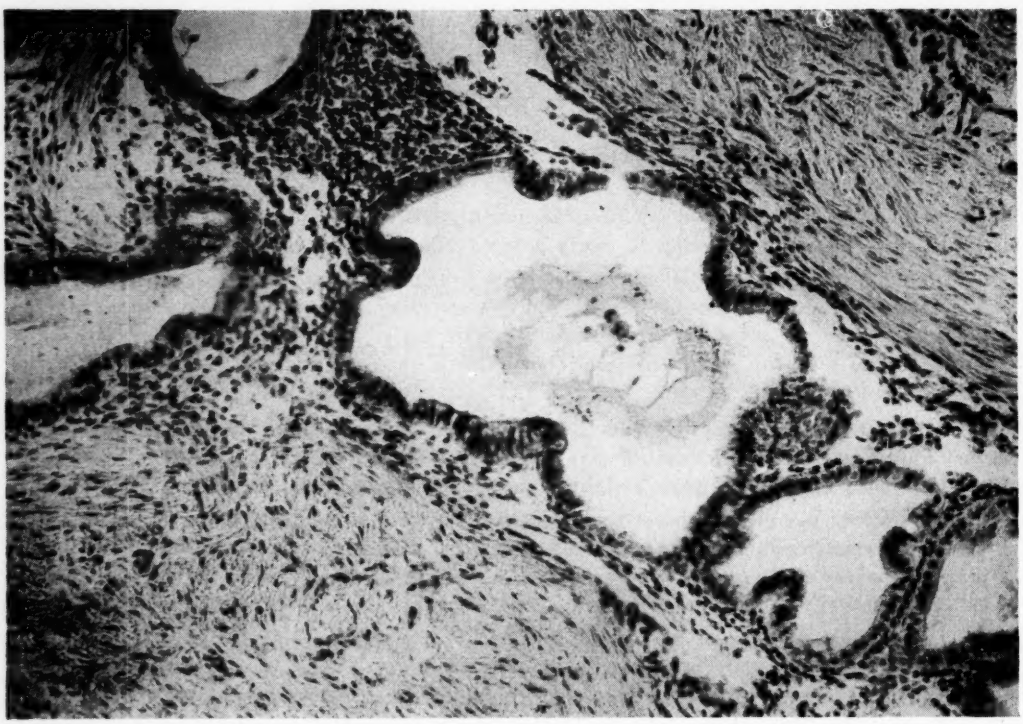

Fig. 1.—Photomicrograph revealing the dark-staining, dense endometrium-like stroma surrounding the glands, some of which contain old blood.

Since 1921, following Sampson's[3] classic description of this condition, the etiology of endometriosis has been a subject of great dispute. Sampson advanced the theory that implantation of endometrial particles in abnormal areas was the result of retrograde menstruation.

Novak[1] and others, on the other hand, have objected to Sampson's theory on the following grounds: (1) Retrograde menstruation, while it may occur, is a rare phenomenon, as contrasted with the great frequency of endometriosis. (2) It is difficult to believe that endometrium, which is dead when thrown off, could enter the small uterine orifice of the tube, travel against the current, and still be capable of implanting itself and growing. (3) Experiments in which a

uteroabdominal fistula was created in monkeys, failed to show any development of endometrium in spite of the fact that menstrual blood was emptied freely into the abdominal cavity. (4) Sampson's theory could not explain endometriosis in certain locations, such as that of the umbilicus.

Most of the authors opposed to the implantation theory of Sampson favor the view that the aberrant endometrium has its origin from abnormal differentiation of the celomic epithelium from which all genital mucous membranes arise (the celomic or serosal metaplasia theory). This theory permits the development of endometrium wherever celomic epithelium or vestiges occur; these areas include the pelvic peritoneal surfaces, hernial sacs, and the umbilicus. Stimuli which have been thought to bring about such abnormal differentiation include inflammation and hormonal imbalance.[4]

No single theory can adequately explain the pathogenesis of endometriosis, particularly of the cases reported occurring in the hand, thigh, axilla, lungs, and kidneys.

Recently, however, Javert[6] advanced the composite theory which included concepts from the other theories and may be summarized as follows:

"(1) Endometrium is a benign tissue capable of extra-uterine spread. It undergoes cyclical homeoplasia that may be a factor in the production of endometriosis. (2) Benign endometrial cells are capable of dissemination and metastasis along the same channels followed by endometrial adenocarcinoma. (3) The pattern of dissemination may be partial or complete in the following manner: direct extension into the myometrium, uterotubal junction and adjacent organs; exfoliation of viable (non-menstrual) endometrial cells into the vagina and through the fimbriated ends of the tubes; implantation of these cells on adjacent serosal surfaces; lymphatic metastasis to regional lymph nodes and adjacent organs; hematogenous metastasis to distant locations."

Summary

A case of umbilical endometriosis has been presented. The major theories explaining the pathogenesis of endometriosis have been enumerated and summarized.

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RECOVERY FROM METASTATIC CHORIONEPITHELIOMA FOLLOWING SURGERY AND LONG-TERM ANDROGEN THERAPY

Report of a Case

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REPORT is made of a patient who recovered from chorionepithelioma following surgery and prolonged therapy with large doses of testosterone propionate.*

Case History

Mrs. E. Q., a 28-year-old white woman, was first seen on Feb. 23, 1949. Her chief complaint was vaginal bleeding of three months' duration. The onset of bleeding followed delivery of a full-term normal male infant. Bed rest had not controlled the bleeding. She also complained of a small tumor inside the vagina which was increasing in size.

Physical Examination.—Her weight was 160 pounds and the blood pressure, 130/80. There were moist wheezing râles over both lung fields.

Other positive findings were confined to the pelvis. On the anterior vaginal wall there was a tender, glistening, dark purple nodule approximately 1½ cm. in diameter. The cervix was hypertrophied, lacerated bilaterally, soft, boggy, and severely eroded. The uterus was enlarged approximately one-half and was retroflexed, adherent, and tender to all movement. The posterior cul-de-sac and adnexa were tender to palpation. Diagnosis was made of indirect endometriosis, postpartum contusion with hematoma formation, and retained secundines. The patient was advised to have a dilatation and curettage with excision of the vaginal wall hematoma.

On admission for surgery the red blood count was 2.9 million with a hemoglobin of 10 Gm. The white blood count was within normal limits. On Feb. 28, 1949, the patient underwent dilatation and curettage and excision of the vaginal tumor. On insertion of the uterine probe, bleeding was profuse. Ovum forceps were gently inserted into the uterine cavity for a biopsy. Extensive bleeding followed this procedure. Intramuscular Ergotrate was given and a uterine pack inserted. Postoperatively, the patient received plasma, 1,500 c.c. whole blood, infusions, and daily injections of testosterone propionate, 100 mg.

Pathological Report.—The vaginal tumor measured 1 by 0.5 by 0.4 cm. Microscopic examination showed hemorrhagic tissue covered by vaginal mucosa. The underlying fibromuscular tissue contained a hemorrhagic nodule with intermingled large hyperchromatic cells. Some cells were indistinctly outlined, while others were polygonal with a distinct cell membrane. Langhans and syncytial cells contained nuclei which varied markedly in size and staining, and occasionally exhibited mitoses. Most of the uterine biopsy material was necrotic and hemorrhagic, with cells resembling decidua. There were some nests of Langhans and syncytial cells, similar to those in the vaginal tumor.

Diagnosis.—Chorionepithelioma metastatic to the vagina.

On March 8, 1949, the patient underwent hysterectomy with bilateral salpingo-oophorectomy. The uterus was approximately 2½ times its normal size and hemorrhagic in appearance. On the posterior surface there was a nodule measuring approximately 2½ cm. in diameter. This was of brownish sheen and appeared to be of old hemorrhagic origin. Further examination disclosed two other similar nodules. The right ovary contained two hydatid cysts of Morgagni. The left ovary and both tubes were normal. Another nodule approximately 3 cm. in diameter was observed in the rectum near the rectosigmoid junction. On palpation, the liver surface was free of nodules. No other implants were observed.

*Testosterone propionate, as Oreton, was supplied through the courtesy of the Clinical Research Division, Schering Corporation, Bloomfield, N. J.

Fig. 1.

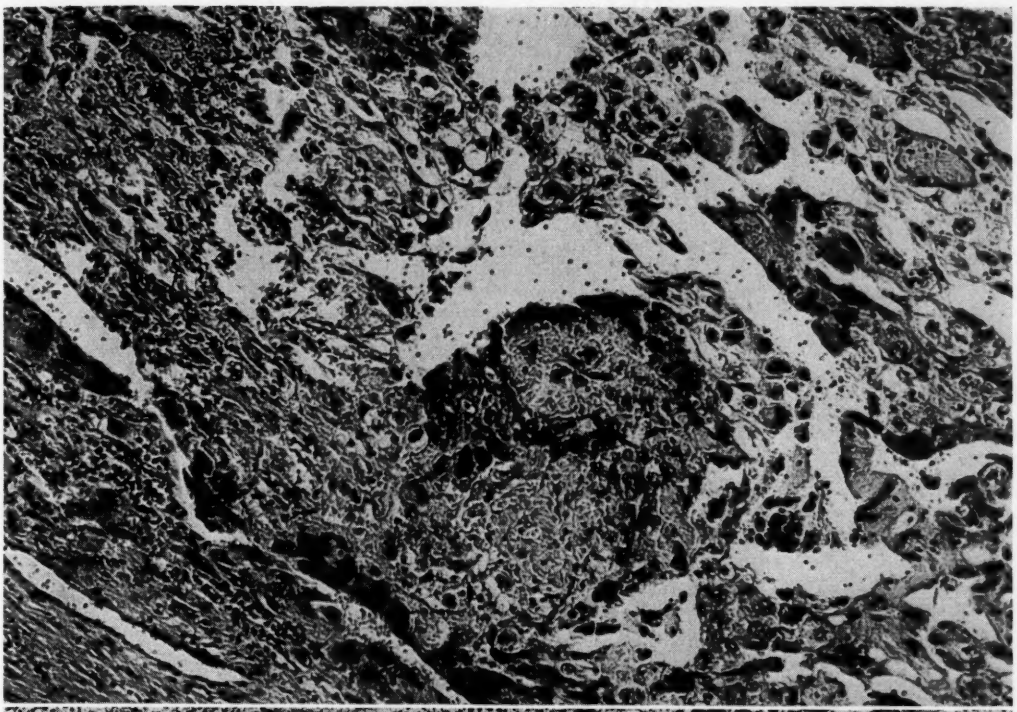
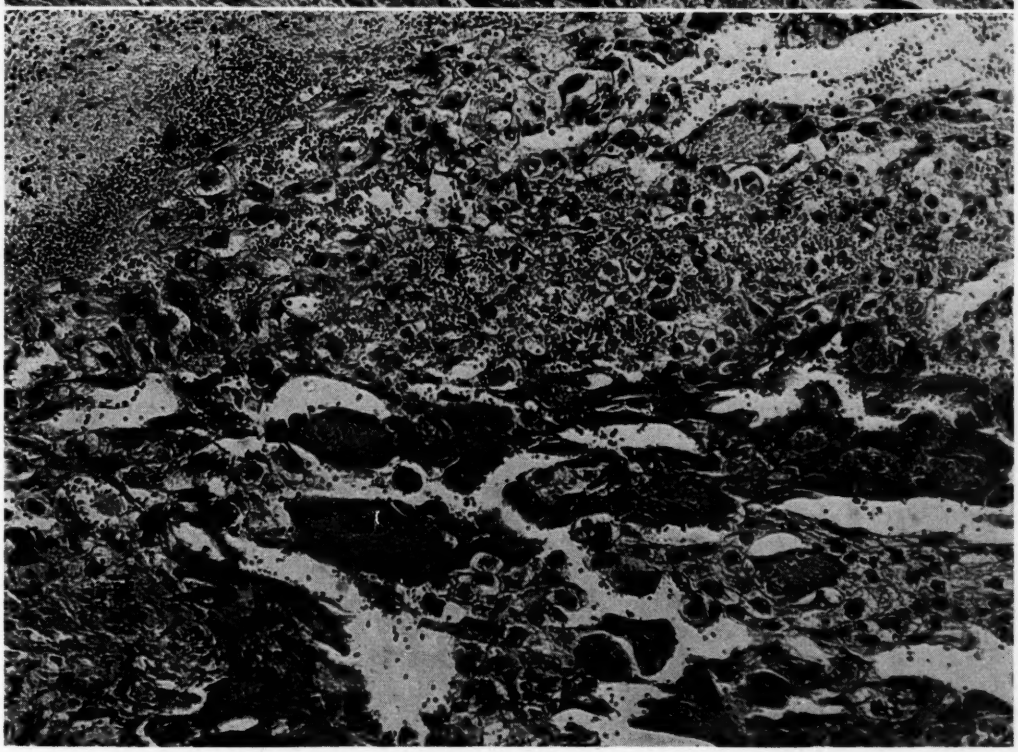


Fig. 2.



Figs. 1 and 2.—Sections through the hemorrhagic mass within the uterine cavity. Degenerated blood clots contain areas of chorionic epithelium. Large cytoplasmic masses of syncytium with intermingled Langhans cells may be seen invading the myometrium. Diagnosis: chorionepithelioma.

When the uterus was freed from the broad ligament, the metastatic nodule in the rectum could be better observed. It involved the entire wall of the rectosigmoid junction. Because of its extensiveness and the copious bleeding, a panhysterectomy was deemed inadvisable. Therefore, a supravaginal technique was carried out. Posterior cul-de-sac tissues were extremely friable and suturing was practically impossible. The wound was closed in the usual manner. In spite of blood loss, the patient withstood the procedure well. The postoperative course was uneventful. Testosterone propionate, intramuscularly, 100 mg., was continued each day, plus 3 Oreton Buccal Tablets, 10 mg.

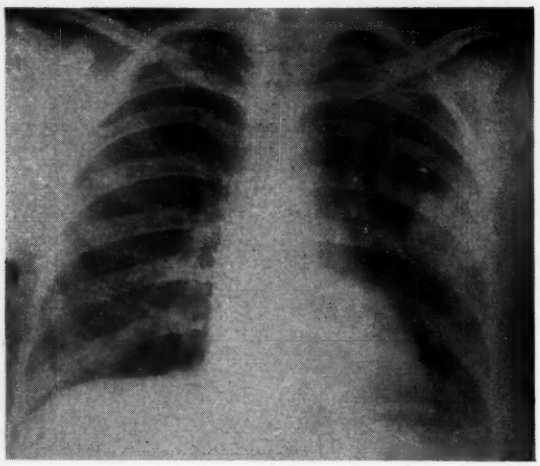


Fig. 3.—March 12, 1949. A round shadow in the left lung field was interpreted as a neoplasm, probably metastic.

Pathological Report.—The uterus weighed 248 grams and measured 10 by 9 by 6 cm. The corpus was distended with a brownish-red, necrotic, friable mass about 4.5 cm. in greatest dimension. This mass extended irregularly into the myometrium and approached the serosa at the fundus where it was separated from the external surface by a very thin layer of myometrium. The lower posterior wall on the left contained a large hemorrhagic mass projecting beneath the serosa and measuring 3.5 cm. in diameter. A similar subserosal nodule was located in the myometrium of the lower right posterior wall. This measured 2.5 cm. in diameter. Another subserosal hemorrhagic nodule 1.5 cm. in diameter was located at the fundus.

Both ovaries were moderately cystic but showed no hemorrhagic lesions. The right ovary contained two large, smooth-lined, thin-walled cysts, each about 2 cm. in diameter, and a large corpus luteum about 1.5 cm. in diameter. Sections through the hemorrhagic mass within the uterine cavity showed degenerated blood clots containing areas of chorionic epithelium. Large cytoplasmic masses of syncytium with intermingled Langhans cells invaded the myometrium (Figs. 1 and 2) and extended into degenerated blood clots. Nuclei varied markedly in size, shape, and staining; occasional mitoses were noted. Sections through the hemorrhagic nodules in the myometrium exhibited a similar microscopic appearance.

Diagnosis.—Chorionepithelioma of the corpus uteri, with metastases in the myometrium.

X-rays taken of the chest on March 12, 1949, showed "a round shadow of increased density in the left mid-lung field, situated laterally. The lesion is 4 inches in diameter and probably represents a neoplastic growth" (Fig. 3).

The patient was seen at frequent intervals during the two months following hysterectomy. Daily therapy with Oreton, 100 mg. intramuscularly, was continued. On May 29, 1949, a Friedman test was positive.

X-ray taken of the chest at this time revealed "a slight decrease in the size of the main mass. There appear to be several satellite nodules which may have been present previously, but which were not well shown" (Fig. 4).

The patient now complained of a tender spot in the right groin. Biopsy of a large cystic mass behind the right labium majus and the vaginal wall was performed on June 2, 1949. When opened, the cystic cavity was found to contain 200 c.c. of old clotted blood

Fig. 4. Fig. 5.

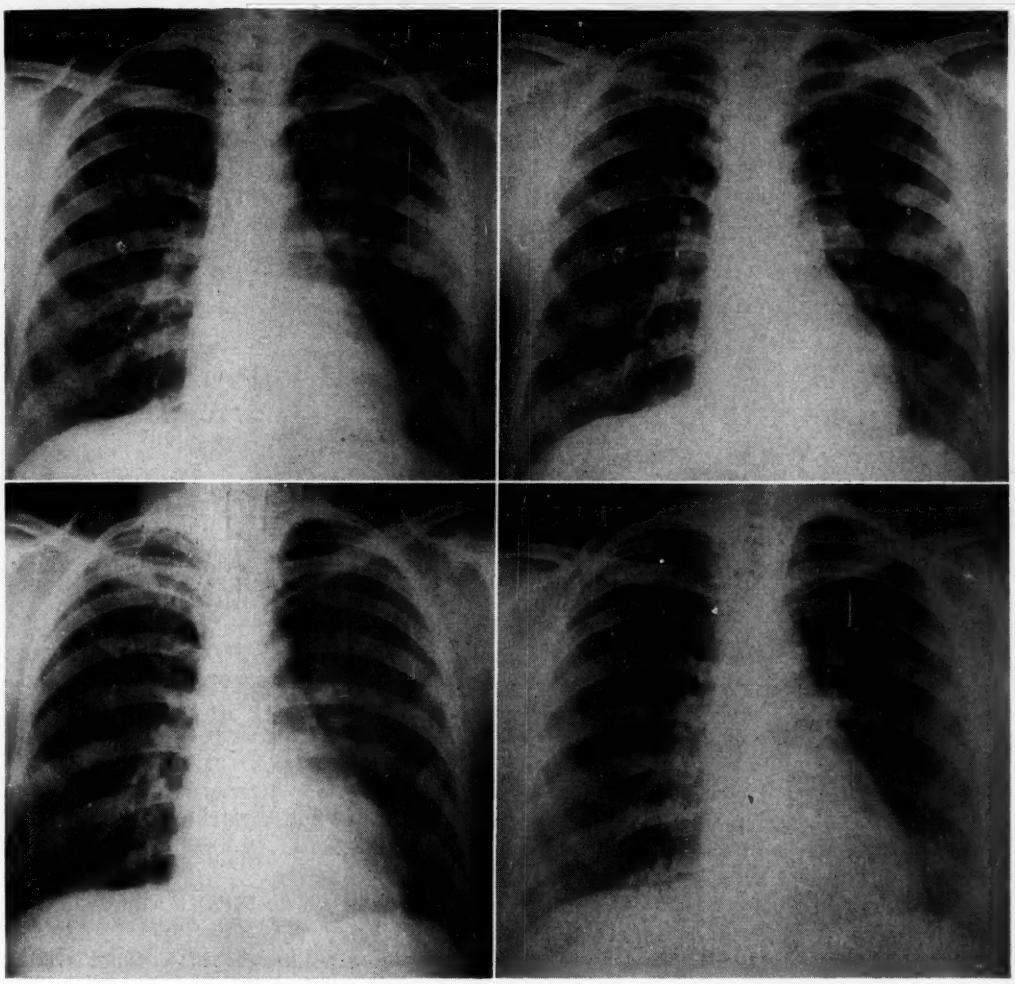


Fig. 6. Fig. 7.

Figs. 4, 5, 6, and 7.—May 19, 1949, June 17, 1949, Oct. 15, 1949, and Feb. 4, 1950, respectively. Showing progressive decrease in size of the lesion.

and a large, friable, polypoid tumor mass. The cavity was large and extended behind the symphysis pubis and up into the pelvis, completely occupying the right ischiorectal fossa. It was impossible to remove this cystic cavity from the vagina. The cavity was packed with several sheets of Gelfoam and closed. The patient withstood the operation well with negligible bleeding.

Pathological Report.—Microscopic examination showed degenerative tissue and blood clots with a nest of pleomorphic cells. Some of these cells were small and round with scant, pale cytoplasm. Others were very large with large, round or ovoid hyperchromatic nuclei and granular eosinophilic cytoplasm.

Diagnosis.—Chorionepithelioma.

X-ray taken of chest on June 17, 1949, revealed a further decrease in the size of the pulmonary lesions (Fig. 5).

On June 28, 1949, a soft, spongy mass protruding from an open sinus on the right vaginal wall was excised. The base of this lesion was hard and irregular in outline, resembling soft cartilage. Oxycel was packed into the bleeding area.

Pathological Report.—Microscopic examination showed granulation tissue and fibrinopurulent exudate with small areas of neoplastic cells. Both Langhans and syncytial cells were present.

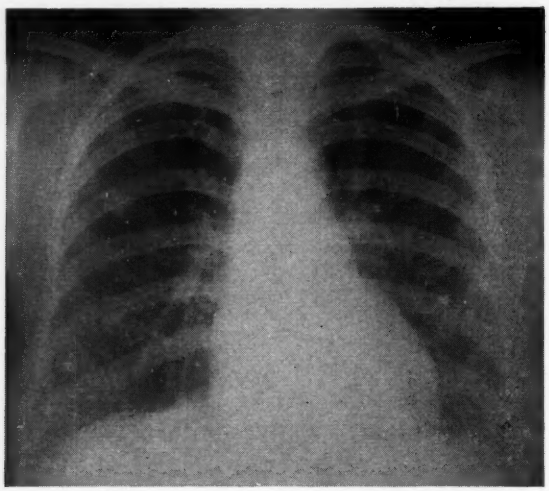


Fig. 8.—January, 1951. Lesion has regressed to a very small density in left lung. This could be tumor residue or small lobular atelectasis secondary to tumor.

Diagnosis.—Chorionepithelioma.

During nine months of treatment with Oreton, 100 mg. daily, androgenic effects became apparent: viz., husky voice, oily skin with acne, plethoric facies, and hirsutism.

X-ray taken of the chest on Oct. 15, 1949, showed the metastatic shadow to be "markedly reduced in size" (Fig. 6).

Oreton therapy was discontinued on Nov. 25, 1949. When she was seen on Jan. 20, 1950, the patient's appearance had reverted to the feminine type with the exception of a persistent huskiness of voice. A typical postoperative menopausal syndrome seemed to be developing. Physical examination at this time was entirely negative.

X-ray taken of the chest on Feb. 4, 1950, still revealed the metastatic shadow. The lesion, however, was less distinct and smaller (Fig. 7).

X-ray taken of the chest in January, 1951, revealed only a very small density in the left lung. This could have been tumor residue or small lobular atelectasis, secondary to tumor (Fig. 8).

After this visit, the patient moved to the West. To date (January, 1954) the patient is living and well, maintaining her weight at 145 pounds. Occasional menopausal symptoms are present sporadically. There are no signs of recurrence.

Comment

Various studies have placed the incidence of true chorionepithelioma (choriocarcinoma) from 1:26,000 pregnancies[1] to 1:60,000 pregnancies.[2] The history is usually that of abnormal pregnancy (hydatidiform mole, ectopic pregnancy, or abortion). About one-fourth of chorionepitheliomas, however, may follow normal pregnancy (1:160,000 pregnancies).

Difficulties in early diagnosis and prognosis are illustrated in almost every reported case. This is due to the nature of the tumor which follows pregnancy and which resembles the trophoblastic tissue of normal pregnancy.

True chorionepitheloma (or choriocarcinoma[3]) is distinguished by a uterus only slightly enlarged, a primary tumor which is limited but infiltrating, absence of stroma and villi, dominance of Langhans and syncytial cells, and metastases which are invariably present. A high or rising chorionic gonadotropin titer is usually found. Necrosis and hemorrhage are dominant because the growth does not carry its own blood supply and must infiltrate and follow the blood stream. The case presented fulfilled the majority of these criteria.

The recovery rate of chorionepithelioma following parturition has been found to be lower than that following abortion or hydatid mole. Most careful classifications usually show choriocarcinomas to be fatal. Dilworth[4] reported that, of 11 cases of choriocarcinoma, all ended fatally.

There are reports in the literature concerning the regression of the primary tumor and/or the metastases.[5-9] In some of these cases extensive irradiation, as well as hysterectomy, was used. Others, however, have reported regression of metastases without irradiation therapy.[7] Novak and Koff[5] reported a case in which autopsy failed to show evidence of chorionepithelioma in the uterus of a patient known to have had uterine tumor tissue previously. Park and Lees[8] reported "Our series gathered from the literature includes 12 cases in which regression of pulmonary metastases was claimed to have occurred. In 8 of these, the evidence offered for the presence of metastases was clinical only: the appearance and cessation of hemoptysis, pain in the chest, etc. In 2 cases, there was, in addition, radiologic confirmation. In the remaining 2 cases there was confirmation from biologic pregnancy tests as well as from roentgenographic appearances." One of the latter patients subsequently died from cerebral hemorrhage due to metastases. In view of the fact that 80 per cent of chorionepitheliomas result in pulmonary metastases, the number of reported regressions is very small. In addition, many of the reports in the literature have a follow-up period of less than six months.

As yet, no good evidence has been presented on which to build a satisfactory explanation for regression of this tumor. Trophoblastic tissue is fetal tissue and therefore a foreign protein, capable of eliciting antibodies.[10] In this manner, the factor of immunity could play a part. Since many regressions of metastases have followed removal of the primary tumor, one might speculate that perhaps the primary uterine growth could maintain metastases. Some have maintained that spontaneous regression does not follow removal of the primary tumor.[11, 12] Removal of the primary tumor in a case with metastases is still indicated,[1, 6] however, and the present report tends to verify this point.

This new growth, so closely associated with pregnancy and endocrine changes, and producing endocrine changes itself, should certainly be considered from an endocrine viewpoint in determining etiology and therapy.[16] The outstanding finding in practically all cases is the extremely high titer of chorionic gonadotropin.

Results of studies with estrogens and other pituitary inhibitors have been discouraging and equivocal. Gagliardi[13] reported chorionepitheliomatous transformation of molar residues in a patient who had received large doses of a stilbene estrogen.

Search of the literature discloses no previous work in this country in which androgens were used against chorionepithelioma in the female. DeGiorgi[14] in Italy used large doses of androgens in the treatment of hydatidiform mole which was followed by chorionepithelioma. The patient died two weeks after panhysterectomy. The use of androgen was mainly palliative.

Marti and Isler[15] in Germany used testosterone propionate and dehydroisoandrosterone, 100 mg. daily, for 10 days against chorionepithelioma in a male. Gynecomastia and testicular pain were reduced while the patient was on androgens. Metastases were not affected, however, and the patient died two years later. The endocrine findings were: high levels of luteotrophic hormone and progresterone, some estrogen, and decreased levels of male hormone.

The rationale for the use of testosterone propionate in malignancies in the female is well substantiated by numerous clinical results and in medical literature. Since chorionepithelioma tends toward overproduction of gonadotropic hormones, testosterone may be used as a pituitary inhibitor, for its increased protein anabolism, and for whatever feeling of well-being it may contribute.

Summary

A case history is presented of a patient with chorionepithelioma following delivery of a full-term normal infant. Histologically verified* metastases were present in the vagina, uterine wall, and ischiorectal space. Biologic tests for pregnancy were positive. Treatment consisted of radical surgery and intensive therapy with testosterone propionate. During this regimen a "cannonball" type of pulmonary lesion, which may be assumed to have been metastatic, regressed.

To date, after five years, the patient is living and well and apparently free of all metastases.

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*Histologic studies were first performed by Dr. John J. Clemmer, of Albany, New York, who made the initial diagnosis of chorionepithelioma. Slides were subsequently reviewed by Dr. John L. Work and Dr. Clarence Miller of Mountainside Hospital, Montclair, New Jersey, who concurred in this diagnosis. At the suggestion of Dr. Work, the slides were forwarded to The Mathieu Memorial Chorionepithelioma Registry in Baltimore, Maryland, where they were reviewed by Dr. Emil Novak, who confirmed the diagnosis of chorionepithelioma.

AMNIOTIC FLUID EMBOLISM

Case Report

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SINCE Steiner and Lushbaugh first described the syndrome of maternal pulmonary embolism by amniotic fluid in 1941, some 30 cases of amniotic fluid embolism have been reported in the literature. The clinical picture of amniotic fluid embolism as described originally has remained largely unchanged. Several common factors are noted in a review of the individual case reports. The patient is generally a multipara in the older age group with an uncomplicated prenatal course and perhaps a postmature fetus or, at least, the fetus is larger than normal. The labor is short, with contractions that are described as being of greater intensity. The first sign or symptom may occur during labor or immediately after delivery. A subjective chilliness has been most commonly reported as the first symptom. Subsequently shock develops with a drop in the blood pressure and the patient then may show signs of anoxia with dyspnea and cyanosis developing. Death may occur in a matter of minutes or in hours. The fetus is usually stillborn or dies within hours after birth.

The pathological diagnosis can be made only by the demonstration of amniotic fluid elements in the small arterioles and capillaries of the lungs. Among the amniotic fluid elements that can be demonstrated are squamous epithelial cells, mucus, and rarely lanugo hairs. In most sections demonstrating intravascular components, large numbers of polymorphonuclear leukocytes are seen.

Gross and Benz centrifuged blood from the inferior vena cava and right side of the heart in one of their cases and demonstrated squamous cells of amniotic fluid origin. They recommend postmortem needle aspiration of the right side of the heart in those cases in which amniotic fluid embolus is suspected, in order to establish, the diagnosis when autopsy is denied.

Examination of other organs shows minor changes consistent with anoxia. Gross examination of the uterus varies in the cases reported. About 50 per cent of the uteri show breaks in the contiguity of the epithelium, either surgical incision or tears extending through the myometrium. Microscopic examination of sections of the uterus may show squamous cells and other amniotic fluid components in the uterine sinusoids or in the pelvic veins.

In summary, the pathological diagnosis of amniotic fluid embolism is made on examination of tissue sections demonstrating amniotic fluid components in the pulmonary vascular system. Gross examination may often be normal or at least the only findings are those of anoxia.

Theories of the pathogenesis of fatal amniotic fluid embolism are concerned with two factors: the entrance of amniotic fluid elements into the maternal circulation and the prime cause of death.

As would be expected, all cases reported at this time have had the common factor of ruptured membranes prior to the development of symptoms of embolization. A high percentage of the patients had contractions which were described as strong or tetanoid. Many of these patients were at or beyond term and the baby was large. One can postulate that the combination of strong contractions, large baby, and ruptured membranes would force amniotic fluid into the uterine sinusoids.

In the case presented in this paper and in more than half of some 23 patients previously reported, the amount of mechanical blocking of the pulmonary vascular system was not sufficient to cause death in itself. It had been originally postulated by Steiner and Lushbaugh that mechanical blocking had been the mechanism of death and that the profound shock was due to an anaphylactoid reaction following entrance of a foreign protein into the maternal circulation.

Weiner and Reid, in a study of the coagulant activity of amniotic fluid, revealed that in an analysis of 22 known cases of fatal amniotic fluid embolism, 13 patients had hemorrhagic manifestations prior to death.

It has been shown that amniotic fluid contains a marked coagulant activity. The factor is similar to thromboplastin in its behavior. Intravenous injection of thromboplastin in large amounts has been shown to cause shock and rapid death in animals. When sublethal doses were given the animals developed shock and the blood became incoagulable. At autopsy these animals showed no thrombi in the major vessels; there were, however, extensive arteriorlar and capillary thrombi in the pulmonary vascular system. Weiner and Reid suggested that amniotic fluid, on entrance into the maternal circulation, would produce intravascular clotting, thereby defibrinating the patient, which might result in postpartum hemorrhage or in other hemorrhagic manifestations.

Ratnoff and Vosburgh, in reporting a fatal case of amniotic fluid embolism, were able to substantiate Weiner and Reid's postulate, by demonstrating the presence of hypofibrinogenemia, possible hypoprothrombinemia, and increased plasma proteolytic activity, prior to the patient's death.

The cause of death in those patients who die shortly after the onset of symptoms and before hemorrhagic manifestation occur may well be consistent with Weiner and Reid's postulate. The following case is briefly reported.

A. W. (U. H. 615-202), a 23-year-old para i, gravida ii, Negro woman was admitted to the staff service of MacDonald House of University Hospitals of Cleveland in prodromal labor in the thirtieth week of gestation. The prenatal course had been normal. The patient's mother died in childbirth. Physical examination on admission was essentially negative. On rectal examination the cervix was 1 cm. dilated and uneffaced. The vertex was 2 cm. above the ischial spines. Morphine and barbiturates were given to forestall labor. About 30 hours after admission, in spite of medication, labor was well established. Rectal examination revealed the cervix to be about 4 cm. dilated. About fifteen minutes later the patient vomited watery green vomitus streaked with bloody mucus. She then complained of a contraction to the nurse in attendance, rolled over on her side, expectorated clear, frothy white sputum, and gasped for breath. The respiratory rate dropped to three to five

per minute and then ceased. The uterus was noted to be tonic. The peripheral pulses were thready. Artificial respiration with positive pressure oxygen was carried out. A cut-down was attempted on the right leg at the ankle. When the vein was incised preparatory to inserting the cannula, it was noted that there was no free flow of blood. Investigation revealed that a clot was present in the vein. The clot was removed. It was some 12 cm. in length and 4 mm. in diameter and a bright red homogeneous color. The patient did not respond to emergency measures and died some fifteen minutes after onset of symptoms. A postmortem section was done and a 1,360 gram living infant was delivered that survived. The amniotic fluid was clear except for two formed, dark red blood clots 5 by 8 cm. in diameter. The placenta had not separated.

Gross examination at autopsy four hours after death was essentially negative. No thrombi were noted in the vessels.

Microscopic sections of the lungs revealed embolic amniotic fluid particulate matter in the small branches of the pulmonary artery in all lobes of both lungs.

In this patient death was probably a result of extensive intravascular clotting. This is substantiated by the demonstration of a formed clot in a leg vein prior to the patient's death. It is of interest that, at autopsy some four hours later, no evidence of intravascular clotting was seen. The fluidity of the blood is due to a fibrinolytic enzyme which can be demonstrated in the blood soon after sudden death.

It has been proposed by Weiner and Reid that heparin be given intravenously as early as possible after recognition of the syndrome. It has been shown that large amounts of thromboplastin are inactivated by small amounts of heparin in vitro. The heparin may therefore prevent further intravascular clotting.

In those patients who survive the initial embolization and who present hemorrhagic manifestations, intravenous fibrinogen in amounts of 4 to 12 Gm. and adequate blood replacement may result in recovery. Recently Reid, Weiner, and Roby reported upon 4 patients with presumptive amniotic fluid embolism and subsequent incoagulable blood who were successfully treated with fibrinogen replacement therapy and blood transfusions.

Conclusion

1. A case of fatal maternal pulmonary embolism by amniotic fluid is presented in which intravascular clotting of blood was demonstrated prior to the patient's death.

2. A plan of therapy including heparin, fibrinogen, and blood replacement is reviewed.

3. The literature is briefly reviewed.

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MULTIPLE EXOSTOSES COMPLICATING PREGNANCY*

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THE occurrence of exostoses in the pelvic bones is uncommon and as a complication of pregnancy causing possible cephalopelvic disproportion is rare. There are very few reports in the literature regarding cartilaginous multiple exostoses in relation to labor. Bessel-Hagan[1] (1891) described seven cases of multiple exostoses, involving the pelvis, complicating labor. Two of the patients died of difficult childbirth. Porak and Daniel[2] (1903) reported a case complicating delivery. Timonen,[3] in 1949, had a case complicated by this disease in which a large nodular exostosis at the junction of the iliac and the pubic bones formed an absolute obstruction to vaginal delivery. He performed a cesarean section after the cervix was fully dilated and he had noted the bony obstacle. The fetus died of intracranial hemorrhage, however. Titus[4] mentions that exostoses of the pelvic cavity are fortunately rare. Kerr and Moir[5] have noted that small osseous growths, if the pelvis is contracted, may cause injuries to the fetal head or lacerations of the uterus.

Cartilaginous multiple exostosis (hereditary deforming chondrodysplasia) is a dominant hereditary disease of bone, transmitted by both males and females. Pathologically and anatomically there is an abnormal production of cartilage by the perichondrium and by the osteogenic stratum of the periosteum of bones preformed in cartilage.[6] Numerous deformities may result, such as bending, shortening, and irregular widening of the metaphysial ends of bone. The disease is usually found in the regions of bone where there is the most vigorous growth. Therefore, involvement of the pelvic bones is unusual. If the pelvis is involved, exostoses may occur at one or more of the osteogenic centers of the pelvis. The primary centers in the pelvis are: the iliac crests, the junction of the iliacs to the pubis, the symphysis, the sacroiliac synchondroses, the sacrum, and the acetabulum. There is no definite pattern in which the pelvis may be affected. An irregular narrowing as a result of the formation of exostotic nodules, bending, and delayed growth in length, may occur. The disease is usually not discovered until puberty because growth of the exostoses is slow and asymptomatic unless pressure develops on nerves, blood vessels, or overlying soft-tissue structures. Growth of the nodules and deformities of bones usually stops after puberty. Any increase in the size of the exostoses or increase in symptoms, after the age of 30, in a previously dormant osteochondroma, may be the first sign of malignant change.[7]

*This work is not to be construed as necessarily reflecting the views of the Department of the Navy.

The following case is that of a patient with multiple exostoses in whom the pelvic exostoses complicated the delivery of her child.

Case Report

M. S. (43395), a 20-year-old white woman, gravida i, para 0, was admitted to the U. S. Naval Hospital, Portsmouth, New Hampshire, Sept. 13, 1953, with irregular mild uterine contractions and leakage of amniotic fluid. The patient was referred from another naval activity where her prenatal course had been uneventful. Her last menses occurred on Dec. 1, 1952 and the expected date of confinement was Sept. 8, 1953. Her past history was not contributory. Family history revealed that her grandfather had "bone trouble." The remainder of the family were normal and healthy.

The patient weighed 118 pounds and was 5 feet, 1 inch, tall. Physical examination was within normal limits except that the upper and lower extremities appeared stunted in growth in relation to the torso. The cervix was 2 cm. dilated with 20 per cent effacement and a vertex presentation was unengaged.

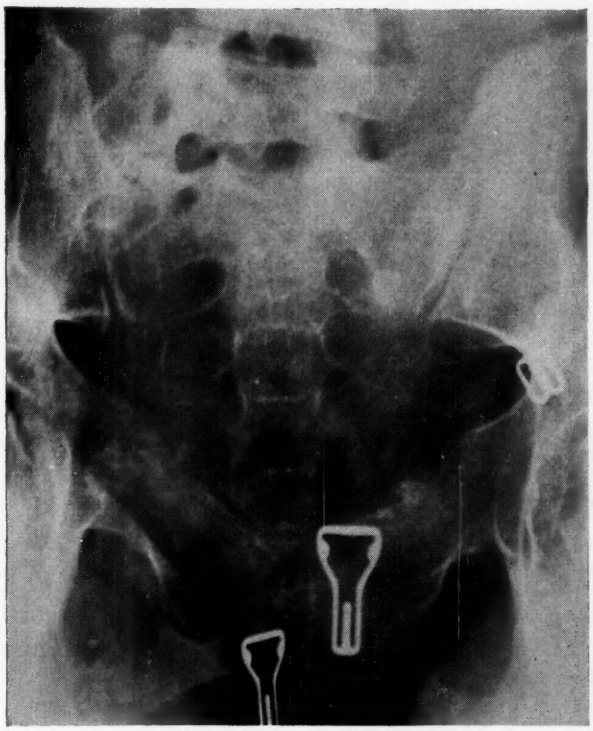


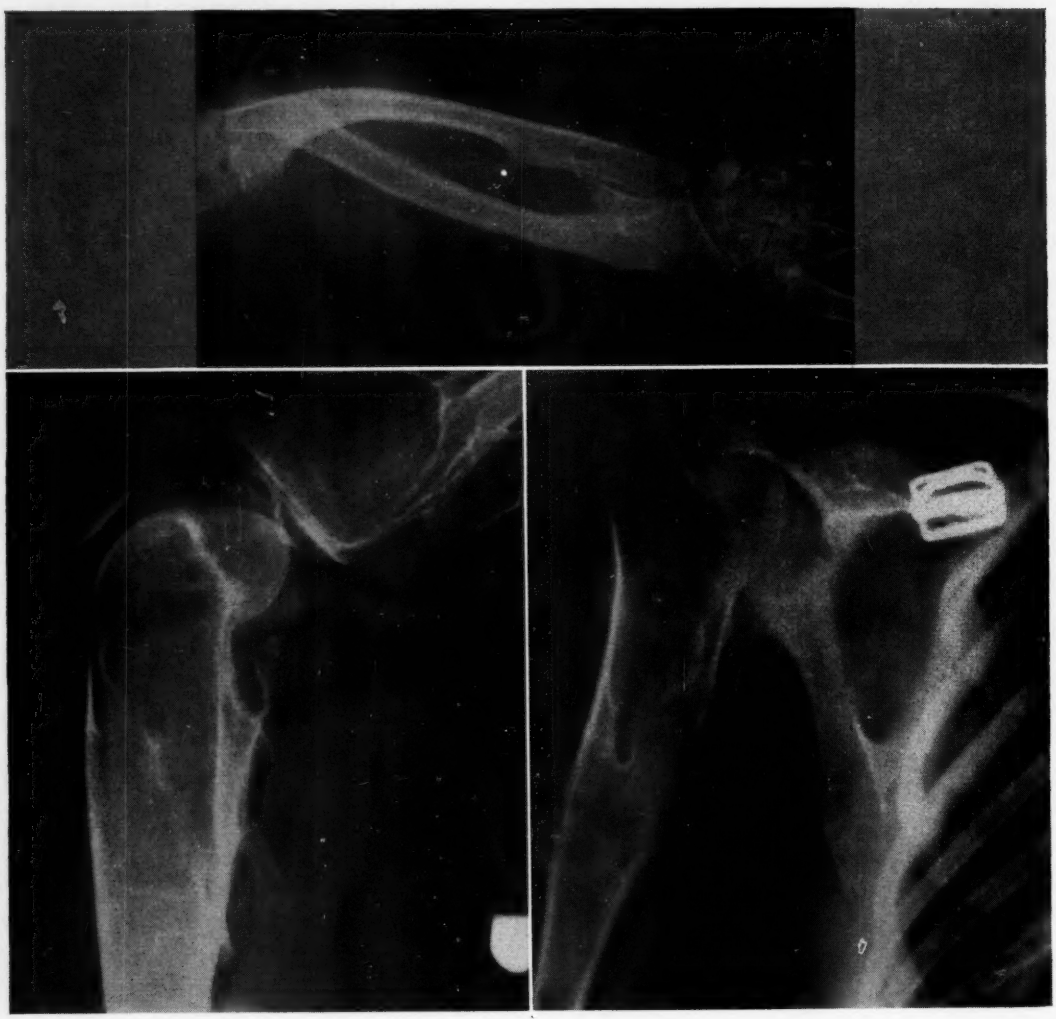
Fig. 1.—Postpartum anteroposterior view showing exostoses of pubic and ischial bones.

Laboratory findings were: blood, type A, RH positive, red cell count 4.51 million, hemoglobin 12.5 Gm., white cell count 10,800, urinalysis was normal. Roentgen pelvimetry according to the Colcher-Sussman method, revealed the following measurements: inlet, anteroposterior 11.2 cm., transverse 11.4 cm.; midpelvis, anteroposterior 11.6 cm., transverse 9.8 cm.; outlet, anteroposterior 6.9 cm., transverse 12.2 cm.; subpubic angle 90 degrees. The pelvic architecture included a round inlet, converging side walls, a good sacral curve, irregularities of the ascending rami of both pubic bones and of the descending rami of the right ischial and right pubic bones (Fig. 1).

Pelvic examination revealed the fetal vertex presenting in right occipitoposterior position at minus 2 station with a borderline cephalopelvic disproportion present. A trial

of labor was felt to be indicated, however. After 12 hours of desultory labor, the cervix was 4 cm. dilated with 50 per cent effacement. An intravenous infusion of 1,000 c.c. of 5 per cent glucose in distilled water was administered in addition to 15 mg. of morphine sulfate, allowing the patient to rest. Eight hours later, strong uterine contractions at five-minute intervals were in effect. The cervix had become completely effaced and 7 cm. dilated. After 6 hours of strong labor, the cervix was fully dilated and the fetal vertex had descended to the ischial spines in the right occipitotransverse position.

A.



B. *C.*

Fig. 2.—*A*, Right forearm. Exostoses of distal radius and ulna with destruction of the distal end of the ulna and bowing of its shaft.

B, Right knee. Several cartilaginous exostoses are seen arising from the distal end of the femur and the proximal ends of the tibia and fibula.

C, Left shoulder. Exostoses of the proximal half of the humerus and the scapula are seen.

After one and one-half hours of the second stage of labor no further progress occurred. The patient was given saddle block anesthesia for delivery. A difficult midforceps operation was performed, with delivery of a normal, healthy, living, male infant who weighed

4,030 grams. The forceps procedure consisted of a classical application of Kielland forceps to the right occipitotransverse position. Attempt at rotation to occiput anterior was unsuccessful. Descent of the vertex occurred only in the right occipitotransverse position with traction on the forceps. It was not until the occiput had reached the outlet of the mother's pelvis that rotation could be performed. The usual perineotomy was done. Inspection of the birth canal did not reveal any soft tissue lacerations. The puerperium was uneventful.

Subsequent osseous roentgenographic survey of the patient revealed the diagnosis of multiple exostoses. Both humeri had several exostoses arising from the upper third of the shafts. The forearms showed exostoses arising from the distal portions of the radii and right ulna. The head of the right ulna had been destroyed by the disease process and there was bowing of its shaft (Fig. 2, *A*). Shortening of the necks of both femora was present with slight coxa vara deformity. Exostoses were seen arising from the distal ends of the femora, the proximal and distal ends of the fibulae and tibiae (Fig. 2, *B*). The disease involved all of the long bones as well as several bones of the hands and feet, and the pelvic bones. X-rays of the newborn infant and of the patient's mother were normal.

Comment

Cephalopelvic disproportion secondary to multiple exostoses is an uncommon complication of pregnancy. Injury to the fetus or to the uterus can occur. Previous authors have reported disastrous results to the mother and to the child. By clinical pelvic evaluation it may appear that the pelvis is adequate for vaginal delivery but occult exostoses may be a cause of obstruction. X-ray pelvimetry will reveal any abnormal osteogenic growths of the pelvic bones which may be present.

Summary

1. Multiple exostoses are described with particular reference to the pelvis.

2. A recent case is presented with multiple exostoses of the pelvis in which vaginal delivery was performed without injury to the mother or child.

3. An obstetrical patient with multiple exostoses should be examined for possible pelvic exostoses because of their potential danger.

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TRANSITIONAL HYDATIDIFORM MOLE ASSOCIATED WITH EXTENSIVE HYDATID DEGENERATION OF THE PLACENTA AND A WELL-DEVELOPED FETUS

Report of a Case

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THIS is a report of a case of a large hydatidiform mole associated with extensive hydatid degeneration of the placenta and a well-developed fetus. The occurrence of this combination is rare. Greenhill[4] has stated, "A fetus is seldom found when a hydatidiform mole is present." A review of the literature over the past thirty-five years did not reveal a case with exactly identical features. Several cases were noted, however, which were similar. Bowles[2] reported a case of "Extensive Hydatidiform Mole Formation With Living Child," and he stated, "In 9,501 deliveries at the Queen's Hospital, Honolulu, from 1932 to 1941, there was only one recorded instance of a single ovum with coexisting fetus and hydatidiform mole." Cline[3] reported a case of "Hydatidiform Degeneration of Placenta, Complete With Fetus." Mueller and Lapp[6] reported a case of "A Single Ovum Pregnancy, With Marked Molar Degeneration of the Placenta, Terminating in Birth of a Living Child." Beltz and Hutchins[1] reported a "Coexisting Hydatidiform Mole With a Living Child and Placenta Praevia."

Clinical Course

The patient was a 26-year-old pregnant white woman, para iii, gravida iv. Her prenatal course was uneventful until approximately the sixteenth week of gestation when she suddenly developed abdominal pain and cramps. These symptoms abated with conservative management only to recur 48 hours later with profuse vaginal bleeding, shock, and finally the spontaneous passage of a well-developed but nonviable fetus, followed by a placenta and approximately 1 gallon of fluid and grapelike vesicles.

Uterine scrapings seven weeks after this episode revealed no residual molar tissue.

Physical examination twelve weeks after the spontaneous abortion revealed a normally regressed uterus and a decrease in size of the patient's previously cystically enlarged ovaries.

Regular monthly quantitative Friedman tests have been negative.

Pathological Examination.—

Fetus: The fetus was a well-developed male that measured 18 cm. from crown to heel, 13 cm. from crown to rump, and weighed 140 grams (Fig. 1). There were no external or internal abnormalities noted at necropsy and the fetal age was calculated as approximately sixteen weeks, in accordance with the outlines of Potter.[7]

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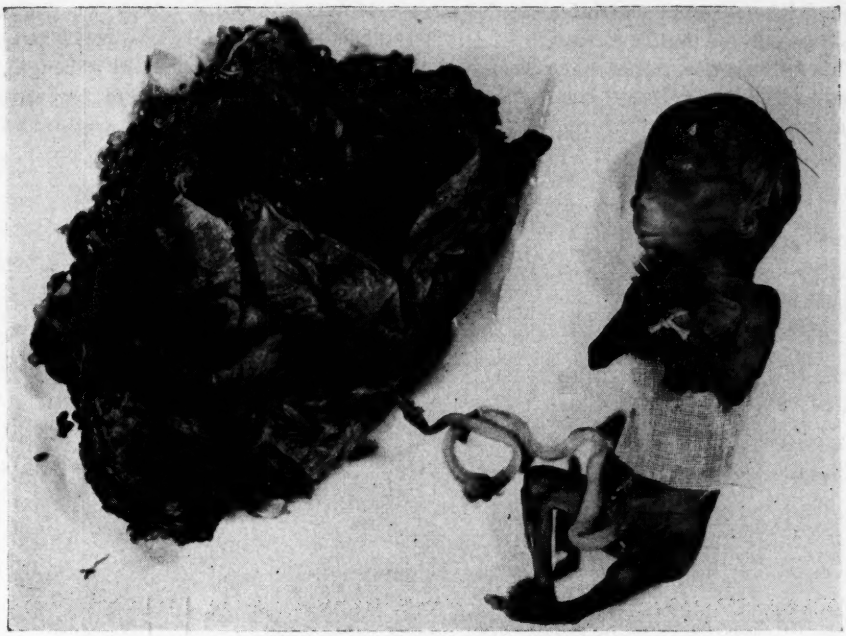

Fig. 1.—Fetus with placenta attached. Transparent and opaque cystic structures occupy large areas of the placenta.

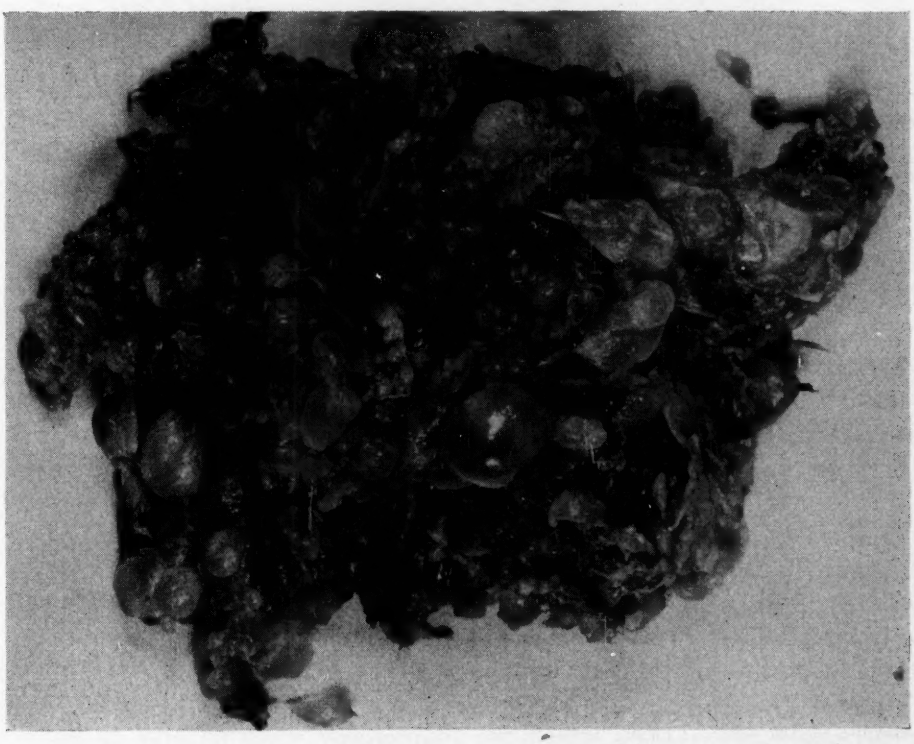

Fig. 2.—Hydatidiform mole, expelled following the placenta in Fig. 1. Decidua and fibrin are noted between the vesicles.

Placenta: The placenta measured 12 cm. in diameter and consisted of usual placenta admixed with adherent, variable-sized gray vesicular structures which were filled with clear, straw-colored fluid.

The microscopic appearance varied from the usual-appearing villi through various intermediary forms to huge edematous cystic villi, many of which were fenestrated. A striking and prominent feature was the absence of visible intravillous capillaries in the cystic villi.

Fig. 3.

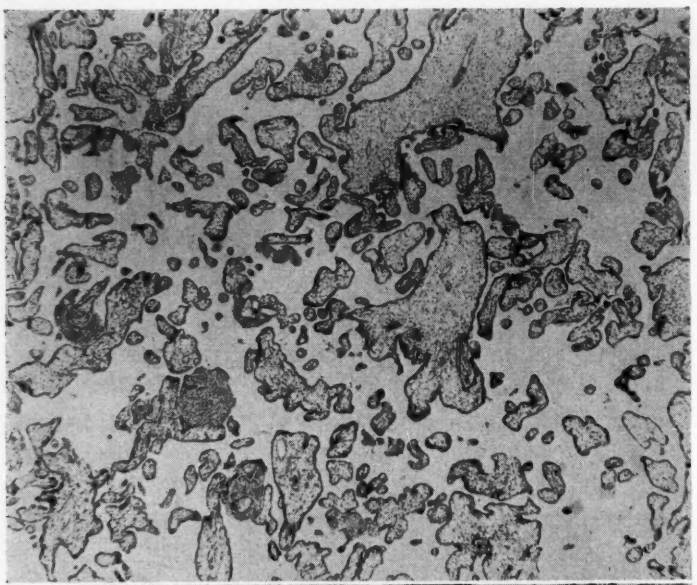

Fig. 4.

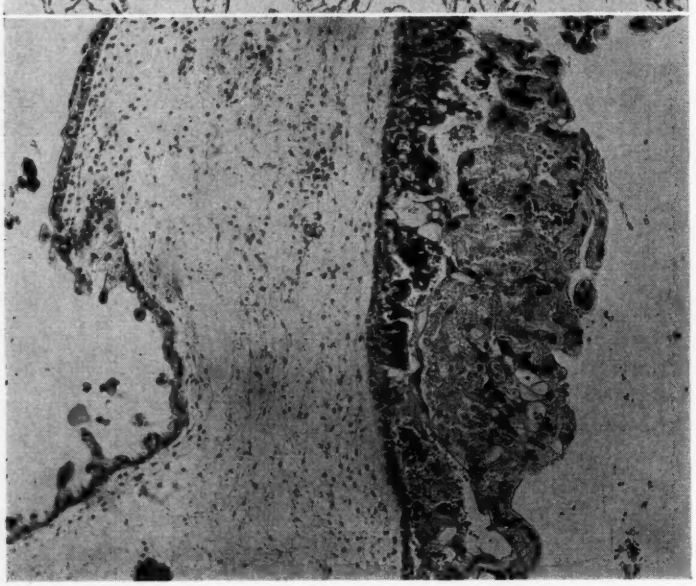

Fig. 3.—Section of transitional areas of placenta showing usual villi as well as larger edematous cystic villi. (×100; reduced ⅓.)

Fig. 4.—Section of avascular villus, cystically distended with edema fluid and covered by a thick mantle of syncytial and cytotrophoblastic cells. (×440; reduced ⅓.)

Hydatidiform mole: The molar tissue consisted of approximately 1 gallon of cystic grapelike structures hung together by hemorrhagic stalks of thin connective tissue. The vesicula structures measured from less than 1 cm. in diameter to over 3 cm. in diameter (Fig. 2).

Histologically the vesicles were similar to those in the placenta except that here many villi were covered by a thick mantle of cytotrophoblastic and syncytial cells.

Comment

This appears to be a case of transitional hydatidiform mole. The term transitional is used in the same manner as it was used by Hertig and Edmonds[5] in reporting "The Genesis of Hydatidiform Mole." These authors have described this type of mole as abortuses averaging sixteen and sixth-tenths weeks in duration. Grossly, they are defined as "abortuses in which various portions of the ovum (chorion, villi, amnion, and embryo) can still be identified but in which enough villi have sufficient hydatidiform degeneration to make the diagnosis clearly evident from the gross specimen." Transitional stages were noted between early hydatidiform degeneration in the villi and classic hydatidiform mole in 15 pathologic ova described in their report.

In our case transitional stages are noted between early hydatidiform degeneration of the villi of the placenta (Fig. 3) and the true hydatidiform mole (Fig. 4). The possibility exists that this was a twin pregnancy with the mole developing in the associated placenta with subsequent death and absorption of the fetus. This seems unlikely in this case as no remnants of a second placenta were noted and because of the transitional stages from normal villi to true hydatidiform mole seen in the placenta still attached to the fetus.

It is interesting to speculate as to the contents and the histologic structure of the cysts or other enlargement present in each ovary. It is also of interest to speculate as to the hormonal relationship between the cystic ovaries and the hydatidiform mole. In our case the ovaries grew smaller after expulsion of the mole.

This case supports the contention that a fetus can live while getting nourishment from only a portion of the placenta even though a part is hydatidiform. That this is the case has also been shown by others.[1, 2, 3, 6]

The rarity of this type of lesion is emphasized by Williams,[8] Greenhill,[4] and others. Williams reported in 1918 that no instance of a viable fetus had been found together with hydatidiform mole formation of the placenta in 17,930 obstetrical cases treated in Johns Hopkins Hospital.

Summary and Conclusion

A case of transitional hydatidiform mole characterized by extensive hydatidiform degeneration of the placenta and a well-developed fetus is presented. The dynamic sequence of events in this case appears to be that the fetus and placenta at first developed in the usual manner but that sometime during development a hydatidiform change gradually took place in the placenta. The fetus lived as long as there was enough functioning placenta to maintain it, and, when there was no longer sufficient placenta, the fetus died and the pa-

tient aborted. In addition to this, as a factor in bringing about abortion, was the mechanical distention of the uterus by the large amount of mole tissue.

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INTESTINAL OBSTRUCTION FOLLOWING THE USE OF A WATER-SOLUBLE CONTRAST MEDIUM (MEDOPAQUE-H) IN HYSTEROSALPINGOGRAPHY*

Case Report

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HYSTEROSALPINGOGRAPHY has been employed for over 40 year as a diagnostic and therapeutic aid. The ideal medium has been sought for many years. In 1914, Rubin[1] and Cary[2] independently reported the use of Collargol in intrauterine and tubal diagnosis. Later, halogen solutions such as sodium iodide, sodium bromide, strontium iodide, and others were tried but were found to be too toxic. In 1926 Heuser[3] introduced iodized poppy seed oil (Lipiodol) as a new medium in hysterosalpingography. The use of this radiopaque material was considered such a great improvement over previous preparations that, in 1932, Campbell voiced the opinion of his day when he stated that Lipiodol was nonirritating, nontoxic, and presented minimal discomfort and danger to the patient. Undoubtedly Lipiodol played a great part in the development of hysterosalpingography, but after its use in a large number of cases, numerous toxic reactions and complications were reported.

Unfavorable occurrences such as foreign-body reactions, allergic phenomena, caseous degeneration of the tubes, acute salpingitis, fever and chills, jaundice, pelvic abscesses, bacterial and chemical peritonitis, and oil embolism were reported frequently enough to indicate that this medium was not an ideal one.[4-11] Considerable proof was presented to show that the oil remained in the pelvic tissues for years, being broken down and absorbed at a rather slow rate. Two hundred laparotomies following Lipiodol salpingography were reported by Schultze[4] in 1932. He found a film of oil over the omentum and the abdominal and pelvic peritoneum in every case. He described areas of yellowish plaques and recent tissue degeneration over the posterior surface of the uterus, broad ligaments, and abdominal peritoneum. Lash[10] reported finding dense omental and parietal peritoneal adhesions in a pelvis following a hysterogram done twenty-two months before the operation.

The artificial production of tubal occlusion due to Lipiodol inflammatory reaction has been cited by Rubin.[6] Reichle and Rottger,[9] and others. A large number of cases of adhesions and foreign-body reactions that occurred after a long interval have been reported. This proves that the reaction to iodized

*Presented at a meeting of the Obstetrical Society of Philadelphia, March 4, 1954.

oil is a slow process, usually occurring after the nonabsorbable oil has been present in the pelvis for a considerable length of time. Cases of oil embolism have been reported, some fatal, others nonfatal. Symptoms and signs vary from chest pain, hemoptysis, chills, fever, to positive pulmonary x-ray findings.[5]

Thus, with these reports in the literature, a concentrated effort was made to develop media which would be less toxic. By 1938, nonoily water-soluble radiopaque media were introduced as an answer to the problem.[12] These media combine a water-soluble organic iodine compound with a vehicle to enhance its viscosity.[16-19] Skiodan (iodomethane sulfonate with acacia) was found to be nonirritating, rapidly absorbed, and radiopaque. In less than one hour the material cannot be visualized by x-ray. Skiodan is excreted by the kidneys, and acacia by the liver and intestinal tract, all traces disappearing after 72 hours. A number of similar water-soluble media have been introduced in the past ten years, all having the advantages of Lipiodol, but lacking the toxic properties previously mentioned. Some newer water-soluble compounds recently developed and employed are Rayopaque with polyvinyl alcohol, sodium ortho-iodohippurate with carboxymethyl cellulose,[12] and polyvinyl pyrrolidone (PVP) with sodium acetrizoate.[14]

To our knowledge no fatalities or serious complications have as yet been reported with the use of the water-soluble radiopaque materials. Such occurrences as venous intravasation, allergic reactions, sudden faintings, and the spread of infection have been reported but these are not as serious or numerous as were reported in the use of oil preparations. Burger[16] reported the experimental production of pelvic inflammatory reaction and pelvic adhesions with high dosages of water-soluble media in animals. With moderate dosages, he reported the disappearance of all inflammatory signs at the end of twelve hours following intraperitoneal injection.

Despite the relatively nontoxic background exhibited thus far by the water-soluble contrast media in vivo, a complication following the use of one of these is documented in the following case presentation.

Mrs. M. T., a 28-year-old gravida 0, para 0, was first seen on July 29, 1953. Her husband was sterile. The purpose of her visit was to discuss the problem of heterologous artificial insemination. After a discussion of all its aspects, she and her husband decided to have the necessary studies preliminary to insemination. Consequently, a protein-bound iodine test was performed which was reported as normal and an endometrial biopsy was reported as showing secretory endometrium. Her last menstrual period occurred from July 31, 1953, to Aug. 6, 1953. On Aug. 8, 1953, using Medopaque-H* a routine hysterosalpingography was performed under the usual aseptic conditions. The dye immediately flowed through the uterus and Fallopian tubes, exhibiting bilateral tubal patency. The patient had an immediate reaction of severe abdominal pain. She went home and thereafter called us frequently because of severe and almost intractable pain which did not respond to the usual oral analgesics. On Aug. 15, 1953, an examination revealed no abnormal findings. On Aug. 21, 1953, she returned for re-examination because of persistence of lower abdominal pain. She stated that she had bled profusely on August 18 and 19, but that the pain was now less intense. At this time it was noted that the abdomen was flat but there was marked peritoneal rebound tenderness. Persistalsis was normal. A cystic mass located

*Medopaque–H, made by Bell-Craig, Inc., New York, consists of sodium ortho-iodohippurate as contrast agent and sodium carboxymethyl cellulose as viscosity vehicle.

posterior to the uterus was thought to be bowel. Her temperature was now elevated. Our impression at this time was that this patient had a chemical peritonitis, secondary to the water-soluble dye used in the hysterosalpingography.

In view of the peritoneal signs, she was placed on oral penicillin for five days. Subsequently, the patient did not return until the time of her admission to the hospital almost two months later. In the interval, about a month after the hysterosalpingography, it was reported by the patient's family physician that she had pleurisy for which treatment was administered. She had been invalided for two months since the original hysterosalpingography. She was unable to take part in her normal household activities, or to pursue her occupation as a secretary. Each night, because of severe pain, it was necessary for her family physician to administer analgesics. For one week prior to admission the patient had had normal bowel movements; these, however, were attended by flatulence and pain. Thirty-six hours before admission to the hospital she began to vomit greenish brown material. In view of the persistent pain and vomiting, the patient was admitted to the hospital on Sept. 30, 1953, for diagnosis and treatment.

The abdominal pain was severe, continuous, and generalized. Examination revealed a young, well-nourished woman in some apparent distress. The lower abdomen was distended, but not markedly so. The percussion note was dull in the right lower quadrant of the abdomen. No muscle guarding or rigidity was present. Peristalsis was present ranging from normal to hypoactive. No high-pitched takeoff or persistaltic rushes could be heard. The white blood count was 14,500 with 86 per cent neutrophils. Our diagnosis at this time was intestinal obstruction due to (1) possible chemical peritonitis; or (2) a band of adhesions following an appendectomy one year previously. Intubation was achieved and antibiotic therapy was begun. The following day x-ray examination revealed distended small bowel in the right upper quadrant and epigastrium. The decision for surgery was made at this time. Her preoperative studies were as follows: sedimentation rate 31 mm. in 1 hour; hemoglobin 14 Gm., red blood count 4,190,000. The white blood count was 11,100.

Laparotomy was performed on Oct. 2, 1953. The obstructed distal ileum was isolated and followed for fifteen inches into the pelvis where several separate adhesions of agglutinative type were found, binding down the bowel and angulating it severely. These adhesions were present on the posterior rim of the pelvic inlet, the posterior surface of the right broad ligament, and on a loop of small bowel just under the projection of the fimbria of the right Fallopian tube, but not adherent to it. These agglutinative adhesions (in contradistinction to the fibrinous variety) separated easily on manipulation and dissection, whereupon gas and fluid within the distended loop immediately passed into the distal ileum and cecum. The obstruction was unquestionably relieved. Before closing the abdomen the cecum was examined carefully in view of the previous appendectomy. No abnormalities were present in this region. The patient made an uneventful recovery, and was discharged on the eleventh postoperative day.

Comment and Conclusions

In view of the fact that this patient was in good health before the hysterosalpingography and in view of the suddenness of onset of the symptoms, particularly the incessant and continuous abdominal pain, we feel safe in directly attributing the development of intestinal obstruction to the diagnostic procedure. Because of the type and location of adhesions in the pelvis, we must assume that we were dealing with a particular and peculiar type of peritonitis. The problem resolves itself to what type of peritonitis we were encountering. If we had employed iodized oil the answer would have seemed quite adequate, namely, that of tissue reaction to a foreign body (iodized oil), and the development of adhesions. The chest symptoms could be explained on the basis of possible showers of oil emboli and the mass in the pelvis on the basis of an oil

cyst as reported by Lash[10] in 1930. We had used Medopaque-H in our hysterosalpingogram, however, and as yet, to our knowledge, no such similar reaction has been reported with the use of any of the new nonoily preparations, including this one. In fact, members of our service had employed Medopaque-H in over 100 cases before this complication occurred, and we have continued to use it in a significant number of cases thereafter.

The question arose as to whether we were dealing with a low-grade bacterial peritonitis. Lash stated that injection of a liquid medium may carry along infected secretion from the cervix or tubes into the peritoneal cavity, thus producing infection. These infections vary in severity from the acute exacerbative variety to the chronic low-grade type. The following facts were in disagreement with such a diagnosis or conclusion, however: 1. The pain and general symptom complex had appeared suddenly after the hysterosalpingogram and continued constantly thereafter. 2. There was a conspicuous absence of fibrinous adhesions, and exudate on laparotomy. 3. There was minimal leukocytosis. 4. There was an absence of residual tubal disease. 5. The patient had received antibiotics in adequate dosage for six weeks.

In rebuttal of an argument for chronic tuberculous peritonitis were the following facts: (1) negative purified protein derivative test; (2) negative history for tuberculosis; (3) paucity of adhesions; (4) absence of visible tubal or adnexal disease; (5) absence of nodularity over the pelvic peritoneum; (6) absence of ascites. These facts, with particular reference to the absence of typical fibrinous thickening in the pelvis, proved to us that we were not dealing with a bacterial peritonitis, tuberculous or otherwise.

We concluded, therefore, that we were dealing with a residue of a chemical peritonitis produced by Medopaque-H, with resultant intestinal obstruction.

In summary, we believe we have encountered a single case of chemical peritonitis, forming peritoneal and intestinal adhesions, with secondary bowel obstruction. The existing facts lead us to believe that this peritonitis was directly due to the water-soluble radiopaque medium, Medopaque-H, which affected the pelvis, peritoneum, and several loops of small bowel lying in the cul-de-sac and just beneath the fimbria of the Fallopian tube.

Until now, gynecologists and radiologists alike have felt that the general complications and toxicity presented by oil salpingography were almost eliminated with the advent of the water-soluble, nonoil media, and we have been using the new media with minimal fear because of their reputed lack of toxicity. In presenting this case we hope to alert the gynecologist, radiologist, and surgeon to possible similar occurrences in using any water-soluble radiopaque medium.

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Department of Reviews and Abstracts

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Selected Abstracts*

Fertility and Sterility

Vol. 5, No. 3, May-June, 1954.

Simmons, Fred A.: Editorial: The Hypogonadal Male, p. 201.

Macdonald, Jean, and Harrison, R. G.: Effect of Low Temperatures on Rat Spermatogenesis, p. 205.

Frank, Irwin N., Benjamin, John A., and Segerson, James E.: Cytologic Examination of Semen, p. 217.

Oettle, A. G.: Morphologic Changes in Normal Human Semen After Ejaculation, p. 227.

Lindahl, P. E., and Kihlstrom, J. E.: An Antiagglutinic Factor in Mammalian Sperm Plasm, p. 241.

Russell, Murray: Can Male Infertility Be Prevented? Major Causes and Therapy, p. 256.

*Rubin, I. C.: Combined Use of Uterotubal Insufflation and Hysterography With Suction Endometrial Biopsy: Condensed Procedure for Sterility Investigation, p. 263.

*Rutherford, Robert N., and Banks, A. Lawrence: Semi-adoption Techniques and Results, p. 271.

Slechta, Robert F., Chang, M. C., and Pincus, G.: Effects of Progesterone and Related Compounds on Mating and Pregnancy in the Rat, p. 282.

Rubin: Combined Use of Uterotubal Insufflation and Hysterography With Suction Endometrial Biopsy: Condensed Procedure for Sterility Investigation, p. 263.

For the benefit of sterility patients whose time is very limited, the author proposes a quick method of investigation. During one visit, between the sixteenth and eighteenth days of the menstrual cycle, three major investigative procedures are done in continuity. A uterine cannula with a 2 by 2 mm. opening at its tip and 2 by 4 mm. openings at its sides, is used. It remains in situ until the last test, suction biopsy of the endometrium, is done. With this cannula, good specimens of endometrium are obtainable. Even at this early time, they should reveal the early secretory changes which follow ovulation. The author states that at this time of the cycle, biopsy cannot interrupt a chance pregnancy because the fertilized ovum is still in the Fallopian tube. He does not discuss the possible risk to this same fertilized egg by the passage of gas through the Fallopian tubes. Insufflation is done first and a kymographic tracing is obtained. If the result is normal, hysterography is done. If insufflation demonstrates tubal obstruction, hysterosalpingography is done. By using Salpix† as the contrast medium, the patient may be released

*Titles preceded by an asterisk are abstracted below.

†Iodine in a water-soluble base.

from study when the dye is absorbed, within an hour or two. The combination of the three procedures induces very little discomfort, the patient being able to leave the table immediately after they are done.

PAUL TOPKINS, M.D.

Rutherford and Banks: Semi-adoption Technics and Results, p. 271.

From the psychological point of view, the results with artificial insemination are just as satisfactory as the results with conventional adoption. During the past thirteen years, the authors have observed no untoward emotional reaction in successfully inseminated women or their husbands. A total of 64 cases of artificial insemination is reported. There were 27 conceptions, an over-all success rate of about 42 per cent. By excluding the 23 discouraged patients who did not persist with insemination, the success rate rose to 66 per cent. The authors emphasize the extreme care with which they selected the proper donors. As a result, their eugenic results were superior to their statistical results. In one case, they matched the red hair of the husband in 2 successive children. In another case, the children manifested physical characteristics recognizable to everyone acquainted with the family. The average number of inseminations necessary to achieve impregnation was 9.4. No mention is made as to how many inseminations were given per month. The authors do say, however, that they mixed the specimen of the donor with that of the sterile husband, but they confess that they do not know why they did it.

PAUL TOPKINS, M.D.

Vol. 5, No. 4, July-August, 1954.

Rubin, I. C.: Uterotubal Insufflation: Value in the Treatment of Tubal Obstruction to Ovular Migration, p. 311.

*Davids, Arthur M., and Bellwin, Alexander: Reconstruction of Fallopian Tubes by Vein and Artery Transplants, p. 325.

Comninos, A. C.: Salpingostomy: Treatment of Female Sterility, p. 334.

*Ten Berge, B. S., and Tik Lok, T.: Plastic Surgery of Closed Tubes With Chorion-Amnion, p. 339.

Bunge, R. G., and Sherman, J. K.: Liquefaction of Human Semen by Alpha-amylase, p. 353.

Sherman, Jerome K.: Freezing and Freeze Drying of Human Spermatozoa, p. 357.

Lane, Frederick E.: Artificial Insemination at Home, p. 372.

Frank, Richard, and Guterman, Henry S.: Comparison of Progesterone Preparations in Secondary Amenorrhea, p. 374.

Maqsood, M.: Role of Thyroid on Maturity and Fertility in the Male, p. 382.

Davids and Bellwin: Reconstruction of Fallopian Tubes by Vein and Artery Transplants, p. 325.

Dogs were operated upon under intravenous Nembutal. The femoral vein was mobilized, ligated, and removed for a distance of about 4 inches. Occasionally, the femoral artery was also removed. The vessel was then placed in warm normal saline and stripped of blood. The vein usually shrank to one-half its original length, much more than the artery. The abdomen was opened and the Fallopian tubes removed. About one inch of uterine horn was opened and the endometrium excised. The vein or artery was then implanted into the uterus and maintained in situ with very fine catgut. It was then fixed along the exposed uterine muscle and mesosalpinx by fine sutures through the adventitia. In some animals, bilateral vein implants were done; in others, a vein and an artery were used. In one-half the number of cases, polyethylene tubing was placed through the vessel into the uterine cavity and sutured with fine silk. The uterine muscle

was then sutured around the transplanted vessel. The dogs were then examined, from one to four weeks postoperatively, and all transplants except one artery were found to be patent and normal. Microscopic examination of grafts excised seven weeks after operation revealed normal intima and media. Veins proved to be more satisfactory than arteries for transplants. The authors discuss the possibility of utilizing saphenous vein grafts in the human being when huge hydrosalpinges are present, thereby precluding a successful tubal plastic operation. They describe in detail how to proceed with the operation in such patients.

PAUL TOPKINS, M.D.

Ten Berge, and Tik Lok: Plastic Surgery of Closed Tubes With Chorion-Amnion, p. 339.

Preliminary experiments in the peritoneal cavity of rabbits demonstrated that human chorion-amnion was an effective barrier against the formation of adhesions. Microscopically, it was observed that there was replacement of the cuboidal epithelium by a layer of collagen fibers. Human chorion-amnion was then obtained during cesarean section. It was washed in sterile normal saline and placed in a sterile solution of glycerol and sodium chloride containing penicillin and streptomycin. It was kept under refrigeration and allowed to thaw slowly several hours before being used for the salpingoplasty. The closed fimbriated ends of the Fallopian tubes were mobilized and opened. Patency was demonstrated by insufflation. Streptomycin powder was spread over the tubes and ovaries. The chorion-amnion membrane, after having been fastened with the aid of a frame, was then sutured around the adnexa with catgut. When extensive hydrosalpinx was found, the tubal plastic operation was not done. Subsequent tests for tubal patency were done with water-soluble contrast medium. In 1951, 6 patients were treated in this fashion. Although during the following year no pregnancies occurred, tubal patency could be demonstrated in 5 of the 6 patients. Later investigation by the authors has shown that the much thinner amnion is even more satisfactory than chorion-amnion membrane.

PAUL TOPKINS, M.D.

Arquivos de clínica ginecológica

Vol. 5, 1952.

*Ribeiro, Edgar da Rosa: Abdominal Pregnancy, p. 79.

*Ferreira, Clarice do Amaral, Bittencourt, Lourdes, and Moreira, Avani: A Ten-Year Report on the Sterility Outpatient Department of the Institute of Gynecology of the University of Brazil, p. 109.

*Couri, Adib Antonio: Treatment of Urogenital Fistulas, p. 117.

*Leite, José: Experiences of the Operative Risk of Gynecologic Surgery in 77 Patients With Cardiac Disease, p. 125.

Ferreira, Clarice do Amaral: Colpocytological Studies From the Gynecological Clinic at the University of Brazil, p. 137.

Ramos, A. Vespasiano: Ovarian Insufficiency, p. 141.

Ribeiro: Abdominal Pregnancy, p. 79.

The author reports two cases of abdominal pregnancy, in one of which the fetus was term sized, but in which fetal death and mechanical ileus had supervened before the patient was first seen. The second patient had an early secondary abdominal pregnancy presenting a syndrome mimicking that of pelvic inflammatory disease. Both patients recovered uneventfully. The author gives a very complete review of pertinent points in symptomatology, differential diagnosis, and treatment of this entity. He stresses the importance of taking a careful history, and indicates that the history of a previous tubal abortion associated with a syndrome suggestive of an abdominal castastrophe connected with pregnancy should awaken a very strong suspicion of secondary abdominal pregnancy. Although in general the author believes it best to leave the placenta in place and close the abdominal wall without drainage, he states that, when the fetus has been dead for some time, with the aid of such prepara-

tions as Gelfoam and Oxycel, resection of the placenta with suture of the superficial bleeding areas may sometimes be feasible. This was done in the author's second case without untoward consequences.

DOUGLAS M. HAYNES, M.D.

Ferreira, Bittencourt, and Moreira: Ten-Year Report on Sterility Outpatient Department of the Institute of Gynecology of the University of Brazil, p. 109.

This is a statistical report on the experience accumulated during the first ten years of activity of the outpatient infertility clinic of the Institute of Gynecology at the University of Brazil. During this period, 200 patients were investigated from the point of view of infertility, and, of these, 35 per cent failed to return for completion of the work-up. Of these patients, 31.5 per cent permitted completion of the investigative part of the study, but failed to return for suggested treatment. At the time the article was written, 13.5 per cent were still under treatment. Of the 20 per cent who followed the treatment prescribed after diagnostic studies had been completed, one-fifth became pregnant; this represented a total of 8 pregnancies in 200 patients studied. Of these 8 patients, only 5 went on to term. The over-all incidence of term pregnancies in this clinic population following a ten-year continuous clinic activity was, therefore, only 2.5 per cent success in terms of full-term pregnancies. Although several reparative operative procedures were undertaken in this time, none of the patients operated upon became pregnant, the successful cases representing patients whose management had been exclusively nonsurgical.

DOUGLAS M. HAYNES, M.D.

Couri: Treatment of Urogenital Fistulas, p. 117

The author reports upon 36 patients with different types of urogenital fistulas, upon whom a total of 53 operations were performed, 41 of them by the author himself. The distribution of the fistulas was as follows: ureteroabdominovaginal, 1; ureterovesicovaginal, 2; ureterovaginal, 2; vesicovaginal, 23; urethrovesicovaginal, 5; urethrovaginal, 3. Of these fistulas, 63.8 per cent were of obstetrical origin, while 27.7 per cent were postoperative complications. In presumptive etiology, 8.3 per cent were inflammatory. Thirty-six of the operative procedures were performed by the vaginal route, 4 transvesically. Miscellaneous plastic operations of specialized types were performed on the remaining 13 patients. Twenty-five of the patients had a single operation only; 7 patients required two procedures; 2 patients were operated upon three times; and 2 patients submitted to four separate operative attacks.

From his large experience, the author draws a number of practical clinical conclusions. He believes that preoperative preparation of these patients is of very great importance, especially in the case of vesicovaginal fistula, in view of the fact that such lesions often have extensive inflammatory induration which interferes with proper performance of the procedure. The preoperative regimen which he recommends consists of local treatment of all superficial inflammatory and macerated lesions either with estrogenic creams, or by local irrigation with bland antiseptic solutions. The author also administers estrogens by the parenteral route, and employs intensive supportive therapy with multivitamin capsules and a thoroughly adequate diet. He believes that a prolonged preoperative treatment of this nature is less important in the case of ureteral fistulas, since the site of operation in these cases is usually sufficiently far removed from the inflamed and macerated areas which result from constant flow of urine. The author uses standard techniques for the repair of these fistulas, and emphasizes as the all-important point in dealing with vesicovaginal fistulas the complete and adequate mobilization of the bladder around the fistulous opening. Three of his patients had stress incontinence following the repair of a vaginal fistula, and it was necessary to perform a supplementary fascial sling procedure of the Aldridge type. The author stresses the importance of early ambulation, and avoids or shortens postoperative catheterization of the repaired bladder as much as possible. He states

that it has not been his experience that the type of suture material used is of any particular importance, provided that the anatomical features of these plastic operations are properly carried out.

DOUGLAS M. HAYNES, M.D.

Leite: Operative Risk of Gynecologic Surgery in 77 Patients With Cardiac Disease, p. 125.

This paper reports the author's experience with 77 patients with heart disease who presented indications for major gynecologic operation. Seventy-three per cent of the 77 patients withstood the operative procedure satisfactorily. Of the 4 patients who died, 1 had a narrow aortic lumen; another had "persistence of the thymus"; a third had mitral disease with superimposed auricular flutter following cyclopropane anesthesia induction; while a fourth patient had severe hypertensive disease with previous cerebral accident, and died 96 hours after operation from the sequelae of this syndrome. Leite considers history of recent heart attack or cerebral accident associated with cardiac insufficiency to be a contraindication to surgery within 90 days of the episode. Other contraindications to surgery in cardiac patients are failure to respond to the usual treatment of the disease, or obesity, anemia, or malnutrition. These factors were found to be far more significant in regard to the potential capacity of the patient to withstand operative attack than were such factors as age, type of lesion, or the results of special laboratory tests. The author prefers ether-oxygen-helium mixtures to other forms of inhalation anesthetic for these women. He believes cyclopropane to be contraindicated. During the operation, variations in the diastolic tension are far more significant prognostically than variations in the systolic tension. The margin of safety of these patients if they are operated upon without correction of dehydration or malnutrition is considerably narrowed. Finally the author recommends careful individualization of each patient by the consulting internist before surgery is undertaken.

DOUGLAS M. HAYNES, M.D.

Boletin de la Sociedad chilena de obstetricia y ginecologia

Vol. 18, No. 3, June, 1953.

*Figueroa, F.: Cervical Dystocia, p. 59.

Varas, O., and Munoz, W.: Eclampsia in the Maternity Hospital of Concepcion, p. 65.

*Larenas, A., and Varas, O.: Maternal Mortality on the Obstetric Service of the Regional Hospital of Concepcion, p. 75.

Figueroa: Cervical Dystocia, p. 59.

The author reviews 118 cases of so-called cervical dystocia demonstrating what he believes to be a definite clinical entity. He defines cervical dystocia as a syndrome due to constitutional fibrosis of the cervix or to cervical atresia secondary to cauterization or surgical incisions. In the so-called functional type of dystocia, Figueroa believes abdominal delivery is necessary in 90 per cent of the patients. The use of various spasmolytic agents, however, may decrease the incidence of cesarean section, and the author states that in his series vaginal delivery was successfully achieved in 32 per cent of a group in which spasmolytics were used for cervical dystocia, as compared with 8.5 per cent in a group of patients in whom spasmolytic agents were not employed. More than 25 per cent of his patients were elderly primigravidas, and Figueroa believes that these women frequently present tissues of inferior quality or insufficient elasticity for uneventful vaginal delivery. Most of his patients were also of relatively high socioeconomic status, and Figueroa believes that such women have a greater sensitivity to the pains of labor and a strong tendency to functional disturbances of psychosomatic type.

In 92 patients in this series, most obstetricians of the United States would not have made the diagnosis of cervical dystocia in the first place. These were patients with various types of uterine inertia. It is also clear from the statistical tables presented by Figueroa that he considers cephalopelvic disproportion one of the etiological factors of so-called cervical dystocia, citing a figure of 16 per cent for this complication. Of the 65 patients whom he treated with doses of atropine and papaverine, 32 per cent were ultimately delivered

vaginally. No clear distinction is made, however, between the uterine inertia syndrome and soft tissue dystocia, so that evaluation of Figueroa's material is complicated by the semantic confusion which has complicated the general understanding of the term "cervical dystocia."

DOUGLAS M. HAYNES, M.D.

Larenas, A., and Varas, O.: Maternal Mortality on Obstetric Service of Regional Hospital of Concepcion, p. 75.

This is a statistical analysis of maternal mortality on the obstetric service of the Regional Hospital of Concepcion for the years 1945-1952, during which period there were 20,183 live births. There were 154 maternal deaths, or 7.63 per 1,000, related to the gravid state; 120 of these deaths were from direct obstetric or puerperal cause, and the remainder followed complications of pregnancy, such as tuberculosis and heart disease.

Of 1,860 patients with septic abortion, 60 died; so one-half of the deaths from obstetrical causes were the sequelae of infected abortion, an entity which is usually classed with gynecologic statistics in this country. Approximately 40 per cent of all abortions seen on the authors' service were of septic type. Of 220 patients with varying degrees of placenta previa, 5 died (2.27 per cent). There were 78 observed instances of rupture of the uterus (0.38 per thousand live births), with 15 maternal deaths (19.2 per cent). Premature separation of the normally implanted placenta accounted for 5 deaths in 94 patients (2.12 per cent). Postpartum hemorrhage caused a mortality rate of 0.89 per cent (total patients, 509). There were 501 patients with the pre-eclampsia-eclampsia syndrome, 86 of whom demonstrated true eclampsia; 9 patients died. The largest single cause of death was infection, accounting for 62.4 per cent of all deaths from primarily obstetric causes. Mortality of disease concurrent with pregnancy was of the order of 1.69 per thousand viable pregnancies; the commonest cause of death in this category was advanced tuberculosis.

The principal conclusion drawn by the authors is that an intensive campaign aimed at reduction of the incidence of criminal abortion should be the first line of attack in reducing the number of deaths from obstetric causes in Chilean women.

DOUGLAS M. HAYNES, M.D.

Vol. 18, No. 4, July, 1953.

Villavicencio, G., Cabrera, H., and Briones, H.: A Case of Ovary Infection by the Method of Aburel, p. 85.

Koref, O.: Hormonal Aspects in Obstetrics, p. 92.

Vol. 18, No. 5, August, 1953.

*Ramirez, C.: Prolonged Pregnancy; Studies on 1,333 Cases of Prolonged Pregnancy, p. 101.

Ramirez: Prolonged Pregnancy, p. 101.

Ramirez defines prolonged gestation as any pregnancy which has remained undelivered 294 days following the first day of the last menstrual period. He further limits his study to those patients whose normal menstrual cycles had a periodicity of between 28 and 30 days. By these criteria, Ramirez found 1,333 instances of prolonged gestation in 61,142 pregnancies, or 2.16 per cent.

The author stresses that there is no pathognomonic clinical or biologic criterion of prolongation of pregnancy; the best that can be done is to evaluate the reliability of the history and use this as a basis for presumptive diagnosis. Various signs which have been suggested for postulating prolonged gestation include Runge's sign (diminution in the transverse diameter of the abdominally palpable uterus); roentgen signs (evidence of epiphyseal ossification; stereoscopic cephalometry); evidences of fetal distress; decreased irritability of the uterus; and urinary pregnandiol determination. The author stresses that none of these by itself is of very great diagnostic value.

He subjects his material to an extensive and meticulous analysis from many points of view. Some of his salient conclusions are the following: the placenta presents no specific histopathologic findings in prolonged gestation, but in general the placentas of

the material studied had the morphologic characteristics of a somewhat less than fully mature placenta. Urinary pregnandiol excretion may be a useful diagnostic aid. If the titer remains high at the expected date of confinement as calculated by Naegele's rule, gestation is prolonged. In 245 cases, or 18.37 per cent of the author's patients, signs of decreased uterine irritability were present; in only 69 patients, or 5.18 per cent, was the degree of uterine activity as objectively determined found to be normal or increased. Induction of labor in prolonged gestation is less successful than induction at term in patients without prolongation of pregnancy. Thirteen of the author's patients had prolonged gestation on two or more separate occasions.

The author's indications for cesarean section in these patients are the following: cephalic presentation with sagittal suture in the transverse diameter; breech presentation in primigravidas; transverse presentation; face and brow presentation; and floating head past term. He believes that internal podalic version should never be used in delivery maneuvers after a prolonged gestation. In the series reported, the maternal mortality was 0.52 per cent, but none of these deaths was due to the prolongation of the gestation. The fetal mortality was 12.12 per cent, or approximately twice the average fetal mortality for the service from which the cases were taken. The principal abnormalities from which the infants suffered were: livid and pallid asphyxia; dehydration; and partial maceration. One thousand two hundred sixty nine of the infants weighed between 3,000 and 4,500 grams. There was no increase in the percentage incidence of congenital malformations and monstrosities. Ramirez believes that once the perils of delivery have been successfully overcome, the child of a patient who has had a prolonged gestation is not further compromised. The article concludes with a rather extensive discussion of the legal aspects of prolonged gestation, with many references to the civil and penal codes of Chile.

DOUGLAS M. HAYNES, M.D.

Vol. 18, No. 6, September, 1953.

*Elgueta, H., and Pena, G.: Isonicotinic Acid Hydrazide in the Treatment of Uterine and Adnexal Tuberculosis, p. 125.

Figueroa, F., Bordeu, J., and Ugarte, G.: Consideration of Nephrosis of the Distal Nephron in Obstetrics and the Importance of Its Treatment, p. 136.

Villavicencio, G., Cabrera, H., and Saffie, F.: Comatose Eclampsia With Serious Liver Damage Treated With Cortisone; a Clinical Case, p. 142.

Briones, Monsalvez, H.: Genetic and Clinical Considerations of 112 Cases of Maternal-Fetal Incompatibility Through Rh Factors, p. 148.

Monckeberg, G., Moll, N., and Padilla, A.: Causes of Prematurity Among Employees, p. 160.

Elgueta, H., and Pena, G.: Isonicotinic Acid Hydrazide in the Treatment of Uterine and Adnexal Tuberculosis, p. 125.

This is a preliminary communication on the benefit observed in 23 patients with uterine and adnexal tuberculosis treated by isonicotinic acid hydrazide with or without streptomycin and para-aminosalicylic acid. The results obtained in patients with the disease well established and with small adnexal lesions, using doses of 15 to 20 Gm. of isonicotinic acid hydrazide, are similar to those previously observed after administration of streptomycin alone. The authors indicate that in those patients who have slow latent development of the lesion but demonstrate large, extensive adnexal involvement, isonicotinic acid hydrazide should be given in conjunction with both streptomycin and para-aminosalicylic acid. In only 2 of the 12 cases which were studied at operation did sterilization of the tubal tuberculosis occur. The over-all preliminary conclusion is that the surgical treatment of pelvic tuberculosis has not been superseded by treatment with isonicotinic acid hydrazide, at least until more definitive results have been obtained.

DOUGLAS M. HAYNES, M.D.

Vol. 19, No. 1. April, 1954.

*Osvaldo Varas, D., and Washington Muñoz, A.: Considerations on Premature Separation of the Normally Implanted Placenta, p. 10.

*Sáez, Eduardo Valenzuela, and Perez, Guillermo Abud: Immediate Surgical Treatment of Obstetrical Injuries of the Bladder by the Transvesical Approach, p. 29.

Osvaldo Varas and Washington Muñoz: Premature Separation of Normally Implanted Placenta, p. 10.

In 21,108 deliveries at the Regional Hospital of Concepcion, Chile, the incidence of premature separation of the normally implanted placenta was 0.38 per cent. Nearly three-fourths of the patients who suffered from this accident had not received adequate prenatal care. Toxemia of pregnancy was present in slightly over 50 per cent of the patients, but in approximately one-third of the cases it was not possible to state with any precision what the etiology might have been. There were two maternal deaths (2.57 per cent). One of these patients was first seen shortly before death; in the other fatal case, mismanagement of the complication was considered to be probably responsible for death. Both patients who died were undelivered. There were two instances of uteroplacental apoplexy; both patients survived cesarean hysterectomy. Sixty-nine of the 78 patients were delivered spontaneously; internal version was performed three times; and cesarean section resorted to five times. The incidence of puerperal hemorrhage was 14.5 per cent. The over-all fetal mortality was 75.2 per cent. The authors' method of treatment consisted of the use of Demerol and scopolamine combined; when spontaneous labor did not occur, oxytocic stimulation of the uterus was utilized.

DOUGLAS M. HAYNES, M.D.

Sáez and Perez: Immediate Surgical Treatment of Obstetrical Injuries of the Bladder by the Transvesical Approach, p. 29.

The authors report two cases in which a serious injury to the bladder occurred at delivery. One patient had a postpartum laceration of the bladder neck, while the other had a ruptured uterus complicated by a laceration of the bladder. In both cases, prompt laparotomy was done and transvesical repair of the bladder successfully accomplished. The patient with the ruptured uterus was treated by suture of the uterine rupture in addition to the bladder repair. Prior to each procedure, ureteral catheters were inserted, and the authors claim that this precaution was helpful. Mobilization and repair of the bladder were performed as in transvesical repair of vesicovaginal fistula. Suture of vaginal lacerations was not necessary. Adequate bladder drainage following the operation was secured by suprapubic cystotomy as well as the use of the indwelling catheter. Both patients recovered uneventfully. The authors recommend that any bladder injury incurred at the time of delivery be managed in this way, since the exposure obtainable by the abdominal approach is far superior, in their opinion, to that obtainable vaginally. One of the patients had a subsequent pregnancy with vaginal delivery without difficulty.

DOUGLAS M. HAYNES, M.D.

American Journal of Pathology

Vol. 30, No. 5, September-October, 1954.

Lattes, Raffaele, Martin, John R., and Ragan, Charles: Suppression of Cortisone Effect on Repair in the Presence of Local Bacterial Infection, p. 901.

Journal of Gerontology

Vol. 9, No. 4, October, 1954.

Glazier, Frank W., Tamplin, Arthur R., Strisower, Beverly, DeLalla, Oliver F., Gofman, John W., Dawber, Thomas R., and Phillips, Edward: Human Serum Lipoprotein Concentrations, p. 395.

Friedberg, Richard: ACTH Administration, Adrenal Response, and Age, p. 429.

Ackermann, P. G., Toro, G., Kountz, W. B., and Kheim, T.: The Effect of Sex Hormone Administration on the Calcium and Nitrogen Balance in Elderly Women, p. 450.

In Memoriam

JOSEPH LOUIS BAER succumbed to acute leukemia on Dec. 8, 1954. He was born in Chicago on April 29, 1880. After completion of public schooling he entered Cornell University for undergraduate study but returned home to enter the University of Chicago for his premedical preparation. In 1902 he was awarded the degree of B.S. and in 1903 the degree of M.S. He received his medical degree from Rush Medical College in 1904 and then entered the service of Michael Reese Hospital for his internship and resident training. This he followed with a year's graduate study under Bumm in Berlin and Schauta in Vienna. After his return to Chicago in 1908 to enter private practice, he rejoined the staff of the Michael Reese Hospital and in 1936 was appointed Senior Attending Gynecologist and Obstetrician and Chief of the Department of Obstetrics and Gynecology. His colleagues respected and admired him for his skill and his forthrightness, as well as for his ability to teach and to train the residents.

In 1917 Dr. Baer was appointed an instructor in Obstetrics and Gynecology by Rush Medical College and served until 1946, when he was retired as Professor Emeritus. At the fiftieth reunion of his graduating class he received the well-deserved award for distinguished service.

Dr. Baer contributed liberally to medical literature and for many years served on the Maternal Welfare Committee of Cook County, the Infant Welfare Society of Chicago, and the Blue Cross Plan's Board of Directors. The Chicago Gynecological Society, The Chicago Institute of Medicine, and the American Gynecological Society honored him with their presidency. He not only helped in founding the American Board of Obstetrics and Gynecology, but for many years served as its vice-president and a member of its Board of Directors. He was honored by Sigma Xi in 1903 and by Alpha Omega Alpha in 1904. He was a Life Fellow of the American Gynecological Society, the American College of Surgeons, the Chicago Gynecological Society, the Central Association of Obstetricians and Gynecologists, the Illinois State Medical Society, and the Chicago Medical Society.

In 1950 devoted patients and friends endowed a lectureship in his honor known as the Joseph L. Baer Lectures of the Chicago Gynecological Society. No member of our profession could have had a more devoted following than Dr. Baer, and certainly no more devoted associates to help him in caring for them. To be counted among his intimates was a privilege indeed, and, certainly, there was no more sincere friend than Joe Baer.

In his private life, Dr. Baer was the center of a large, diverse, and deeply devoted family to whom he gave aid, comfort, and love without measure. By precept and example he taught his children the art of meeting life's problems with courage and determination. His devotion to his wife, Janet, who survives him, was well known. He had a tremendous capacity for making friends but he never employed it for selfish gain. His colleagues considered him a shining example of an ideal physician and a staunch defender of ethical practice.

Ludwig A. Emge

Correspondence

Progesterone-Induced Withdrawal Bleeding as a Simple Physiologic Test For Pregnancy, A Confirmatory Diagnostic Tool

To the Editors:

I believe the results of a simple physiologic test for pregnancy, consisting of the administration of progesterone to cause withdrawal bleeding in the nonpregnant patient, would be of interest to the reader, especially since the accuracy has been 100 per cent in a series of 18 patients in whom the diagnosis could not be established. The use of progesterone as a diagnostic and therapeutic agent in the management of amenorrhea[1-3] has been evaluated, but the specific application of induced withdrawal bleeding by progesterone as a diagnostic test for pregnancy has not been evaluated. Progesterone was administered orally in 400 mg. amounts daily for three days to 13 patients and intramuscularly in 100 mg. amounts for three days to 5 patients.

	RESULTS		RANGE IN DAYS OF	
	PREGNANT	NONPREGNANT	ONSET OF BLEEDING	DURATION OF BLEEDING
Intramuscularly 5 cases	0	5	7 to 14 (Average 11)	3 to 7 (Average 5)
Orally 13 cases	7	6	2 to 5 (Average 3)	4 to 7 (Average 5)

The amount of bleeding did not exceed what would be considered a normal menstrual period. In the 7 pregnant patients the diagnosis was confirmed by follow-up examination after six or more weeks or by Friedman tests. The test confirmed the presence of a pregnancy in two instances as early as the thirty-sixth day from the first day of the last menstrual period, and the range was from the thirty-sixth day to the sixty-eighth day. The prenatal courses were unaltered and no reaction to the medication was noted.

The cost at present is not in excess of the amount for the routine Friedman test. Undoubtedly the amount of progesterone used in this series is in excess of the actual need, and with further investigation a minimal dosage with optimal accuracy will be determined, and the cost will be greatly reduced.

Whether or not this small series represents a degree of accuracy which will prove incorrect, in the light of current understanding of gynecologic physiology the degree of accuracy is plausible. I feel justified on this basis in recommending the progesterone test as a harmless, highly reliable (even in early pregnancy), and simple physiologic test for confirming pregnancy. Further study is indicated to confirm the accuracy, to establish a minimal dose, and to evaluate the role of combining estrogen and progesterone. Further study may prove this wrong, but certainly enthusiasm is warranted for the present.

GLEN E. HAYDEN, M.D.

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DEC. 19, 1954

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Items

American Board of Obstetrics and Gynecology

The next scheduled Examinations (Part II), oral and clinical, for all candidates will be conducted at the Edgewater Beach Hotel, Chicago, Illinois, by the entire Board from May 12 through May 20, 1955. Formal notice of the exact time of each candidate's examination will be sent him in advance of the examination dates.

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2105 ADELBERT ROAD
CLEVELAND 6, OHIO

Fourteenth British Congress of Obstetrics and Gynaecology

The Fourteenth British Congress of Obstetrics and Gynaecology will be held in Oxford, England, July 27-30, 1955. For information write to

THE CONGRESS SECRETARIES
RADCLIFFE INFIRMARY
OXFORD, ENGLAND

Fifth Spanish Portuguese Congress of Obstetrics and Gynecology

The Fifth Spanish Portuguese Congress will be held at Seville, Spain, April 13 to 16, 1955.

Subjects selected for discussion are:

Portuguese Section

Physiopathology of the Lower Uterine Segment

Spanish Section

Puberty: (1) Morphological Evolution of the Woman in Puberty; (2) Endocrinology of Puberty; (3) Psychology of Puberty; (4) Clinical Aspects of Puberty.

All communications relating to this Congress should be addressed to the Secretary General, Dr. M. Recasens, Calle Munoz Olive, 7, Seville, Spain.